U.S. FOOD & DRUG ADMINISTRATION

2/14/2019

Austin R. Evers
Executive Director
American Oversight
1030 15th Street NW, B255
Washington, DC 20005

Dear Mr. Evers,

The attached records are being provided by the Office of the Chief Counsel (OCC) in partial response to your request 2018-2488 dated March 12, 2018, for records from the Food and Drug Administration pursuant to the Freedom of Information Act to determine whether the opioid manufacturing and distribution industry is influencing federal policy related to opioid abuse, specifically records reflecting communication between (a) any FDA political appointee or member of the Senior Executive Service (SES), and (b) any employee or representative of the following entities and their subsidiaries and affiliates: McKesson Corporation; Purdue Pharma L.P.; Endo Health Solutions, Inc. and/or Endo Pharmaceuticals Inc.; Cardinal Health, Inc.; Johnson & Johnson and/or Janssen Pharmaceutical NV; Mallinckrodt Pharmaceuticals; AmerisourceBergen Drug Corporation; Arnold & Porter Kaye Scholer LLP; Quinn Emanuel Urquhart & Sullivan, LLP; Williams & Connolly LLP, or Covington & Burling LLP.

Your request is granted in part.

After a thorough review of the responsive records, we have determined that portions of the documents are exempt from disclosure under exemptions (b)(4) and (b)(5) of the FOIA, 5 U.S.C. § 552, and have been redacted as delineated below:

- Exemption (b)(4) permits the withholding of "trade secrets" (TS) and "commercial confidential information" (CCI).

- Exemption (b)(5) permits the withholding of inter-agency or intra-agency communications records which are part of the deliberative process and pre-decisional. Disclosure of such material could inhibit the open and candid expression of opinions and diminish the quality of the decision-making process.

OCC considers your request closed. If you have any questions about this response, you may contact Lakita Ross at 301-796-0661 or at Lakita.Ross@fda.hhs.gov. Please be advised that your request may have been submitted to one or more component offices within FDA. Those offices will reply to you directly. **This is not the agency final response and you will receive additional appeal rights with the final response, so**

Office of the Chief Counsel
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

you do not have to act at this time.

Sincerely

David Mednick -S

Digitally signed by David Mednick -S
Date: 2019.02.14 12:15:45 -05'00'

David Mednick
Deputy Chief Counsel

Office of the Chief Counsel
Food and Drug Administration
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AMERICAN OVERSIGHT

Commercial ✓
Expedited/Media
Other

MAR 2 3 2018

March 12, 2018

2018-2488

VIA ONLINE PORTAL

Sarah Kotler
Director, Division of Freedom of Information Office
Executive Secretariat Office of the Commissioner
Food and Drug Administration
12420 Parklawn Drive
Room 1020
Rockville, MD 20857

Re: Freedom of Information Act Request

Dear Ms. Kotler:

Pursuant to the Freedom of Information Act (FOIA), 5 U.S.C. § 552, and the implementing regulations for the Food and Drug Administration (FDA), 21 C.F.R. Part 20, American Oversight makes the following request for records.

The nationwide epidemic of opioid abuse continues to worsen as the Centers for Disease Control and Prevention (CDC) have reported a continued increase in the dramatic number of U.S. opioid overdose deaths.[1] The President's Commission on Combating Drug Addiction and the Opioid Crisis ("the President's Opioid Commission") has recognized that opioid manufacturers, through their marketing and promotion of opioids, have contributed to the current crisis.[2] The President's Opioid Commission further identified the inadequate oversight of opioid drugs by the FDA as another contributor to the crisis.[3]

State and local governments have brought hundreds of lawsuits against opioid manufacturers alleging negligent distribution, misleading marketing and other wrongdoing.[4] Opioid manufacturers

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[1] CENTERS FOR DISEASE CONTROL AND PREVENTION, *Drug Overdose Deaths in the United States Continue to Increase in 2016*, Aug. 30, 2017, https://www.cdc.gov/drugoverdose/epidemic/index.html.

[2] THE PRESIDENT'S COMMISSION ON COMBATING DRUG ADDICTION AND THE OPIOID CRISIS, FINAL REPORT, Nov. 1, 2017, https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf.

[3] *Id.*

[4] Erika Fry, *Big Pharma Is Getting Hit with a Huge Wave of Opioid Suits*, FORTUNE, Sep. 27, 2017, http://fortune.com/2017/09/27/big-pharma-opioid-lawsuits/; Alana Semuels, *Are Pharmaceutical Companies to Blame for the Opioid Epidemic?*, THE ATLANTIC, Jun. 2, 2017,

and distributors have reportedly responded to these government attempts to hold them accountable with political contributions and lobbying.[5] And, FDA Commissioner Scott Gottlieb, who has received payments from opioid manufacturers and distributors,[6] has previously publicly criticized law enforcement efforts to crack down of the industry's harmful practices.[7]

American Oversight seeks records to determine whether the opioid manufacturing and distribution industry is influencing federal policy related to this public health crisis.

Requested Records

American Oversight requests that the FDA produce the following within twenty business days:

> All records reflecting communications (including but not limited to emails, email attachments, text messages, chat or Slack messages, telephone call logs, calendar invitations/entries, meeting notices, meeting agendas, informational material, draft legislation, talking points, any handwritten or electronic notes taken during any responsive communications, summaries of any responsive communications, or other materials) between (a) any FDA political appointee* or member of the Senior Executive Service (SES) and (b) any employee or representative of the following entities and their subsidiaries and affiliates:
>
> 1. McKesson Corporation
> 2. Purdue Pharma L.P. (including any communications from, to or with J. David Haddox);
> 3. Endo Health Solutions Inc. and/or Endo Pharmaceuticals Inc.;
> 4. Cardinal Health, Inc.;
> 5. Johnson & Johnson and or Janssen Pharmaceutica NV;
> 6. Mallinckrodt Pharmaceuticals;
> 7. AmerisourceBergen Drug Corporation;
> 8. Arnold & Porter Kaye Scholer LLP (including emails from any individual with an email address ending in @apks.com or @arnoldporter.com);
> 9. Quinn Emanuel Urquhart & Sullivan, LLP (including emails from any individual with an email address ending in @quinnemmanuel.com);

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https://www.theatlantic.com/business/archive/2017/06/lawsuit-pharmaceutical-companies-opioids/529020/.

[5] Julianna Goldman & Laura Strickler, *Drug Companies Flex Lobbying Muscle in Fight Against State Opioid Lawsuits*, CBS NEWS (Jan. 25, 2018, 7:45pm), https://www.cbsnews.com/news/drug-companies-flex-lobbying-muscle-in-fight-against-state-opioid-lawsuits/.

[6] Lee Fang, *Donald Trump's Pick to Oversee Big Pharma Is Addicted to Opioid-Industry Cash*, THE INTERCEPT (Apr. 4, 2017, 2:15pm), https://theintercept.com/2017/04/04/scott-gottlieb-opioid/.

[7] Scott Gottlieb, *The DEA's War on Pharmacies—and Pain Patients*, Am. Enter. Inst., March 23, 2012, https://www.aei.org/publication/the-deas-war-on-pharmacies-and-pain-patients/.

10. Williams & Connolly LLP (including emails from any individual with an email address ending in @wc.com); or
11. Covington & Burling LLP (including emails from any individual with an email address ending in @cov.com).

*"Political appointee" should be understood as any person who is a Presidential Appointee with Senate Confirmation (PAS), a Presidential Appointee (PA), a Non-career SES, any Schedule C employees, or any persons hired under Temporary Non-career SES Appointments, Limited Term SES Appointments, or Temporary Transitional Schedule C Appointments.

Please provide all responsive records from January 20, 2017, to the date the search is conducted.

In addition to the records requested above, American Oversight also requests records describing the processing of this request, including records sufficient to identify search terms used and locations and custodians searched and any tracking sheets used to track the processing of this request. If FDA uses FOIA questionnaires or certifications completed by individual custodians or components to determine whether they possess responsive materials or to describe how they conducted searches, we also request any such records prepared in connection with the processing of this request.

American Oversight seeks all responsive records regardless of format, medium, or physical characteristics. In conducting your search, please understand the terms "record," "document," and "information" in their broadest sense, to include any written, typed, recorded, graphic, printed, or audio material of any kind. We seek records of any kind, including electronic records, audiotapes, videotapes, and photographs, as well as letters, emails, facsimiles, telephone messages, voice mail messages and transcripts, notes, or minutes of any meetings, telephone conversations or discussions. Our request includes any attachments to these records. **No category of material should be omitted from search, collection, and production.**

Please search all records regarding agency business. **You may not exclude searches of files or emails in the personal custody of your officials, such as personal email accounts.** Records of official business conducted using unofficial systems or stored outside of official files is subject to the Federal Records Act and FOIA.[8] **It is not adequate to rely on policies and procedures that require officials to move such information to official systems within a certain period of time; American Oversight has a right to records contained in those files even if material has not yet been moved to official systems or if officials have, through negligence or willfulness, failed to meet their obligations.**[9]

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[8] *See Competitive Enter. Inst. v. Office of Sci. & Tech. Policy*, 827 F.3d 145, 149–50 (D.C. Cir. 2016); *cf. Judicial Watch, Inc. v. Kerry*, 844 F.3d 952, 955–56 (D.C. Cir. 2016).

[9] *See Competitive Enter. Inst. v. Office of Sci. & Tech. Policy*, No. 14-cv-765, slip op. at 8 (D.D.C. Dec. 12, 2016) ("The Government argues that because the agency had a policy requiring [the official] to forward all of his emails from his [personal] account to his business email, the

In addition, please note that in conducting a "reasonable search" as required by law, you must employ the most up-to-date technologies and tools available, in addition to searches by individual custodians likely to have responsive information. Recent technology may have rendered FDA's prior FOIA practices unreasonable. **In light of the government-wide requirements to manage information electronically by the end of 2016, it is no longer reasonable to rely exclusively on custodian-driven searches.**[10] **Furthermore, agencies that have adopted the National Archives and Records Agency (NARA) Capstone program, or similar policies, now maintain emails in a form that is reasonably likely to be more complete than individual custodians' files.** For example, a custodian may have deleted a responsive email from his or her email program, but FDA's archiving tools would capture that email under Capstone. Accordingly, American Oversight insists that FDA use the most up-to-date technologies to search for responsive information and take steps to ensure that the most complete repositories of information are searched. American Oversight is available to work with you to craft appropriate search terms. **However, custodian searches are still required; agencies may not have direct access to files stored in .PST files, outside of network drives, in paper format, or in personal email accounts.**

Under the FOIA Improvement Act of 2016, agencies must adopt a presumption of disclosure, withholding information "only if . . . disclosure would harm an interest protected by an exemption" or "disclosure is prohibited by law."[11] If it is your position that any portion of the requested records is exempt from disclosure, American Oversight requests that you provide an index of those documents as required under *Vaughn* v. *Rosen*, 484 F.2d 820 (D.C. Cir. 1973), *cert. denied*, 415 U.S. 977 (1974). As you are aware, a *Vaughn* index must describe each document claimed as exempt with sufficient specificity "to permit a reasoned judgment as to whether the material is actually exempt under FOIA."[12] Moreover, the *Vaughn* index "must describe *each* document or portion thereof withheld, and for *each* withholding it must discuss the consequences of disclosing the sought-after information."[13] Further, "the withholding agency must supply 'a relatively detailed

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[personal] account only contains duplicate agency records at best. Therefore, the Government claims that any hypothetical deletion of the [personal account] emails would still leave a copy of those records intact in [the official's] work email. However, policies are rarely followed to perfection by anyone. At this stage of the case, the Court cannot assume that each and every work related email in the [personal] account was duplicated in [the official's] work email account." (citations omitted)).

[10] Presidential Memorandum—Managing Government Records, 76 Fed. Reg. 75,423 (Nov. 28, 2011), https://obamawhitehouse.archives.gov/the-press-office/2011/11/28/presidential-memorandum-managing-government-records; Office of Mgmt. & Budget, Exec. Office of the President, Memorandum for the Heads of Executive Departments & Independent Agencies, "Managing Government Records Directive," M-12-18 (Aug. 24, 2012), https://www.archives.gov/files/records-mgmt/m-12-18.pdf.

[11] FOIA Improvement Act of 2016 § 2 (Pub. L. No. 114-185).

[12] *Founding Church of Scientology* v. *Bell*, 603 F.2d 945, 949 (D.C. Cir. 1979).

[13] *King* v. *U.S. Dep't of Justice*, 830 F.2d 210, 223–24 (D.C. Cir. 1987) (emphasis in original).

justification, specifically identifying the reasons why a particular exemption is relevant and correlating those claims with the particular part of a withheld document to which they apply.'"[14]

In the event some portions of the requested records are properly exempt from disclosure, please disclose any reasonably segregable non-exempt portions of the requested records. If it is your position that a document contains non-exempt segments, but that those non-exempt segments are so dispersed throughout the document as to make segregation impossible, please state what portion of the document is non-exempt, and how the material is dispersed throughout the document.[15] Claims of nonsegregability must be made with the same degree of detail as required for claims of exemptions in a *Vaughn* index. If a request is denied in whole, please state specifically that it is not reasonable to segregate portions of the record for release.

You should institute a preservation hold on information responsive to this request. American Oversight intends to pursue all legal avenues to enforce its right of access under FOIA, including litigation if necessary. Accordingly, FDA is on notice that litigation is reasonably foreseeable.

To ensure that this request is properly construed, that searches are conducted in an adequate but efficient manner, and that extraneous costs are not incurred, American Oversight welcomes an opportunity to discuss its request with you before you undertake your search or incur search or duplication costs. By working together at the outset, American Oversight and FDA can decrease the likelihood of costly and time-consuming litigation in the future.

Where possible, please provide responsive material in electronic format by email or in PDF or TIF format on a USB drive. Please send any responsive material being sent by mail to American Oversight, 1030 15th Street, NW, Suite B255, Washington, DC 20005. If it will accelerate release of responsive records to American Oversight, please also provide responsive material on a rolling basis.

Fee Waiver Request

In accordance with 5 U.S.C. § 552(a)(4)(A)(iii) and 21 C.F.R. § 20.46(e), American Oversight requests a waiver of fees associated with processing this request for records. The subject of this request concerns the operations of the federal government, and the disclosures will likely contribute to a better understanding of government operations by the general public in a significant way.[16] Moreover, the request is primarily and fundamentally for non-commercial purposes.[17]

American Oversight requests a waiver of fees because disclosure of the requested information "[i]s in the public interest because it is likely to contribute significantly to public understanding of the

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[14] *Id.* at 224 (citing *Mead Data Central, Inc. v. U.S. Dep't of the Air Force*, 566 F.2d 242, 251 (D.C. Cir. 1977)).
[15] *Mead Data Central*, 566 F.2d at 261.
[16] 21 C.F.R. § 20.46(b).
[17] 21 C.F.R. § 20.46(c).

operations or activities of the Government."[18] The disclosure of the information sought under this request will document and reveal the activities of the federal government, including whether an agency is communicating with, and being influenced by, opioid manufacturers and distributors in formulating policy to respond to a nationwide public health crisis. And, as described in more detail below, American Oversight's website and social media accounts demonstrate its ability and intention to effectively convey information received to the public.

This request is primarily and fundamentally for non-commercial purposes.[19] As a 501(c)(3) nonprofit, American Oversight does not have a commercial purpose and the release of the information requested is not in American Oversight's financial interest. American Oversight's mission is to promote transparency in government, to educate the public about government activities, and to ensure the accountability of government officials. American Oversight uses the information gathered, and its analysis of it, to educate the public through reports, press releases, or other media. American Oversight also makes materials it gathers available on its public website and promotes their availability on social media platforms, such as Facebook and Twitter.[20] American Oversight has demonstrated its commitment to the public disclosure of documents and creation of editorial content. For example, after receiving records regarding an ethics waiver received by a senior DOJ attorney,[21] American Oversight promptly posted the records to its website and published an analysis of what the records reflected about DOJ's process for ethics waivers.[22] As another example, American Oversight has a project called "Audit the Wall," where the organization is gathering and analyzing information and commenting on public releases of information related to the administration's proposed construction of a barrier along the U.S.-Mexico border.[23]

Accordingly, American Oversight qualifies for a fee waiver.

Conclusion

We share a common mission to promote transparency in government. American Oversight looks forward to working with FDA on this request. If you do not understand any part of this request, have any questions, or foresee any problems in fully releasing the requested records, please contact

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[18] 21 C.F.R. § 20.46(a)(1).
[19] 21 C.F.R. § 20.46(c).
[20] American Oversight currently has approximately 11,800 page likes on Facebook and 40,900 followers on Twitter. American Oversight, FACEBOOK, https://www.facebook.com/weareoversight (last visited Mar. 12, 2018); American Oversight (@weareoversight), TWITTER, https://twitter.com/weareoversight (last visited Mar. 12, 2018).
[21] *DOJ Civil Division Response Noel Francisco Compliance*, AMERICAN OVERSIGHT, https://www.americanoversight.org/document/doj-civil-division-response-noel-francisco-compliance.
[22] *Francisco & the Travel Ban: What We Learned from the DOJ Documents*, AMERICAN OVERSIGHT, https://www.americanoversight.org/francisco-the-travel-ban-what-we-learned-from-the-doj-documents.
[23] *Audit the Wall*, AMERICAN OVERSIGHT, www.auditthewall.org.

Dan McGrath at foia@americanoversight.org or 202-897-4213. Also, if American Oversight's request for a fee waiver is not granted in full, please contact us immediately upon making such a determination.

Sincerely,

Austin R. Evers
Executive Director
American Oversight

Kotler, Sarah

From: American Oversight FOIA <foia@americanoversight.org>
Sent: Friday, March 23, 2018 9:38 AM
To: Kotler, Sarah
Subject: Re: FDA FOIA

Thank you. Yes, that is correct.

On Mar 23, 2018, at 9:37 AM, Kotler, Sarah <Sarah.Kotler@fda.hhs.gov> wrote:

Dear Mr. McGrath,

Based on our conversation, your request for records is limited to the following offices/individuals:

Immediate Office of the Commissioner – Political appointees, SES employees
Office of the Chief Counsel – Political appointees, SES employees
Office of the Executive Secretariat – Political appointees only
Office of the Counselor to the Commissioner - Political appointees, SES employees

Please confirm.

Thanks,

Sarah B. Kotler, J.D.
Director
Office of the Executive Secretariat
Division of Freedom of Information
U.S. Food and Drug Administration
Tel: 301-796-8976
Sarah.Kotler@fda.hhs.gov

<image001.png>

<image002.jpg> <image003.jpg> <image004.jpg> <image005.jpg> <image006.jpg>

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Via E-filing www.regulations.gov

May 8, 2018

Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.

Re: Comment on Citizen Petition, Docket No. FDA-2018-P-1448

On behalf of Purdue Pharma L.P. ("Purdue") the undersigned submit this comment in response to the Citizen Petition filed on behalf of Collegium Pharmaceutical, Inc. requesting, *inter alia*, that the Agency withdraw the abuse-deterrent labeling approved for OxyContin® (oxycodone HCl) Extended-release Tablets, NDA 022272, and consider withdrawing approval of that NDA.

Collegium requests that the Agency withdraw approval for abuse-deterrence labeling for all extended-release oxycodone drug products with physicochemical properties or clinical abuse potential data that are inferior to those of Xtampza® ER (oxycodone) extended-release capsules. The crux of Collegium's argument is that, with the approval of oral abuse deterrence labeling in November 2017, Xtampza has more comprehensive abuse deterrence labeling and is therefore purportedly the gold standard against which the abuse deterrent characteristics of all other extended-release oxycodone products should be measured. With respect to OxyContin specifically, Collegium requests that FDA take steps to revoke the labeling describing the drug's abuse-deterrent features and reconsider the relative benefits and risks of the product.

As FDA has made clear, the developing science of abuse-deterrent formulation technologies is in its early stages. All opioid drug products can be abused and all carry the risk of addiction even under appropriate medical use. The degree to which abuse-deterrent formulations can reduce the risks and consequences of abuse, overdose, and addiction is uncertain. In this context, FDA officials have expressed the need for further development of multiple potentially valuable approaches to formulating drug products to deter their abuse, calling for more, not fewer, such products to be pursued and, when warranted, approved. This is important because, at present and for the foreseeable future, there is not likely to be a basis to conclude that one abuse-deterrent technology is meaningfully better than another in the real-world setting, let alone predict such an

outcome based on pre-market testing. Contradicting these principles, Collegium suggests that, based solely on pre-market tests and approval of an oral abuse deterrence claim for its own product, the labeling and even the approval of other recognized abuse-deterrent formulations should be withdrawn. That suggestion is ill-conceived.

Importantly, Collegium bases its request for FDA action on flawed studies that do not adequately evaluate the abuse potential of Xtampza. Contrary to Agency guidance, the studies Collegium cites did not use the most feasible and efficient means of preparing Xtampza for oral abuse. As outlined in this comment and in the attached study reports, experiments conducted by an independent testing laboratory show that Xtampza can be easily and rapidly extracted in ingestible liquids under conditions that can be readily duplicated in any commonly equipped kitchen. For example, in five minutes or less, the oxycodone content of *unmanipulated* Xtampza beads is easily and substantially extracted into immediate-release form in common, ingestible liquids:

- 99% of the oxycodone content is extracted in one minute in 100 mL Coca-Cola® when held at 95°C with constant stirring
- 90% of the oxycodone content is extracted in 5 minutes in 100 mL of tea when held at 95°C with constant stirring
- 90% of the oxycodone content is extracted in 5 minutes in 100 mL of 95% ethanol when held at 60°C with constant stirring.[1]

These and other data provided in this submission indicate that simple extraction of the oxycodone content into ingestible solvents is the easiest and quickest means of defeating the extended-release, abuse-deterrent properties of Xtampza. Collegium's pharmacokinetic and oral abuse potential studies were performed only on crushed or chewed Xtampza beads and not dissolved Xtampza beads. Because extraction of unmanipulated beads is the easiest and quickest means of defeating the controlled-release mechanism of Xtampza for purposes of oral abuse, Collegium's studies are inconsistent with Agency guidance, which instruct sponsors to study the manipulation technique causing the greatest release of the active opioid ingredient. Thus, the Collegium studies do not comprehensively assess the risk of oral abuse or whether Xtampza provides meaningful deterrence to such abuse. Collegium's current, incomplete, evaluation provides no basis to conclude that Xtampza will be subject to less oral abuse than OxyContin.

Additionally, Collegium's assessment of the potential for alcohol-induced dose dumping also appears to be incomplete and potentially misleading. This is a significant

[1] We are providing a redacted version of this comment for public display on www.Regulations.gov with specific test conditions omitted, to avoid providing a roadmap to would-be abusers interested in defeating the Xtampza formulation. The unredacted version of this comment has been filed with the Agency and also provided to counsel for Collegium.

weakness that implicates patient safety as well as the potential for oral abuse of Xtampza. This submission includes data from *in vitro* dissolution testing conducted by an independent laboratory using media containing ethanol to simulate co-ingestion of unmanipulated Xtampza beads with alcohol. These data show that the extended release properties of unmanipulated Xtampza beads are substantially compromised in the presence of alcohol. These findings raise serious public health and safety issues, as both legitimate patients and abusers may be exposed to oxycodone plasma levels higher than intended in the presence of alcohol, potentially resulting in serious adverse outcomes. Collegium's limited alcohol interaction studies do not appear to adequately assess this risk because, among other reasons, its *in vivo* tests appear to have studied only intact Xtampza, which is in a capsule shell that has limited solubility (and therefore resists dissolution) in alcohol. Xtampza is specifically approved for administration by opening this shell and administering the beads without the shell, and thus the sensitivity of unmanipulated Xtampza beads to alcohol must be evaluated.

Based on the data presented in this comment, there is no basis to conclude that Xtampza has any meaningful deterrence to oral abuse through extraction, and no basis to believe that Xtampza is safer or has more robust abuse deterrent attributes than OxyContin.

The Collegium Petition also makes a number of assertions about the relative resistance of Xtampza and OxyContin to intranasal abuse. Those assertions are premised on false assumptions about the OxyContin intranasal abuse potential study and a flawed comparison of the Xtampza and OxyContin studies. The arguments presented by Collegium provide no basis to conclude that Xtampza is more resistant to intranasal abuse, or any other routes of abuse, than OxyContin.

In sum, Collegium's Petition provides no legitimate basis to revoke the labeling describing the abuse-deterrent attributes of OxyContin or to reevaluate the risk/benefit profile of OxyContin. Purdue therefore respectfully urges the Agency to deny Collegium's requests.

I. Appropriate Testing To Assess Susceptibility To Oral Abuse Must Include Thorough Evaluation Of The Formulation's Vulnerabilities To Multiple Methods Of Preparation For Oral Administration

FDA's Guidance on the evaluation and labeling of abuse deterrent opioid analgesics ("ADF Guidance") acknowledges that all existing approaches to abuse deterrence have weaknesses and limitations.[2] Recognizing that abusers will target and

[2] "[T]he fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because

attempt to exploit vulnerabilities in abuse-deterrent products, the ADF Guidance advises sponsors to subject their formulations to a broad spectrum of experiments intended to simulate potential abuse and tampering techniques. The overall approach recommended is to exhaustively test proposed formulations to identify not just their strengths, but also their vulnerabilities to a range of potential manipulations.[3] This necessarily includes both common means of preparing drugs for abuse, such as those described by abusers in interviews or in online discussion forums, as well as potential new methods of abuse that can be identified through comprehensive iterative approaches that extend testing to failure.[4]

Abuse of opioid drug products through the oral route of administration can take many forms. These include ingestion of multiple intact tablets or capsules as well as ingestion following various types of manipulations that attempt to compromise or defeat the controlled-release or abuse-deterrent technologies used in the drug. Manipulations can include physical manipulations such as particle size reduction or chewing as well as extraction techniques involving intact, manipulated, and/or pretreated tablets or capsule contents in various liquids. A recently published analysis of the specific oral routes

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opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products." Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling (April 2015), p. 2, available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf ("ADF Guidance"). *See also* Statement from FDA Commissioner Scott Gottlieb, M.D. – FDA is taking new steps to help assess opioid drugs with abuse-deterrent properties (June 13, 2017), available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm562961.htm ("Opioid formulations with properties designed to deter abuse are not abuse-proof or addiction-proof. These drugs can still be abused, particularly orally, and their use can still lead to new addiction. Nonetheless, these new formulations may hold promise as one part of a broad effort to reduce the rates of misuse and abuse").

[3] The ADF Guidance provides that the goal of *in vitro* studies is to "manipulate the product to the point of defeating its abuse-deterrent properties." ADF Guidance, p. 6. Further, "[e]xtractability and solubility studies should be designed to determine whether any of the formulation components might be differentially solubilized and extracted, allowing an abuser to bypass the drug's abuse-deterrent properties." ADF Guidance, pp. 6-7.

[4] "Methodologically, [*in vitro*] studies should be designed with knowledge of the physicochemical properties of the product and the methods available to abusers to manipulate the product and should be conducted on the to-be-marketed formulation. Sponsors should consider both the mechanisms by which abusers can be expected to attempt to deliberately overcome the abuse-deterrent properties of the product as well as the ways that patients may alter the formulation (unintentionally or intentionally) that change the rate or amount of drug released (e.g., dose dumping may occur when taking the product with alcohol or when the product is cut, chewed, or crushed). Testing should provide information sufficient to fully characterize the product's abuse-deterrent properties, including the degree of effort required to bypass or defeat those properties. In some cases, when designing *in vitro* studies, it may be useful to obtain information from prescription opioid abusers about how they would manipulate and abuse an abuse-deterrent product." ADF Guidance, p. 6 (emphasis added).

reported by abusers of products designed to be crush resistant, as well as conventional dosage form opioid analgesics without abuse-deterrent characteristics, indicates that individuals orally abuse both categories of products in a variety of ways including swallowing whole capsules, chewing, dissolving in the mouth, and dissolving in liquid and then drinking.[5]

Because oral abuse is not a homogenous phenomenon, an evaluation of resistance to oral abuse must consider the full range of potential manipulations that may precede oral abuse, as informed by available information on the methods likely to be used by abusers and information on the characteristics of the test formulation. To this end, the ADF Guidance calls for a thorough evaluation of the potential to manipulate proposed formulations using mechanical means (particle size reduction) as well as chemical means (dissolution/extraction), taking into account the physicochemical properties of the product, with the overall goal of manipulation to the point of defeat of the abuse-deterrent properties of the formulation.[6] Consideration of the specific test formulation is critical because different patterns of manipulations for oral abuse can be expected with formulations that have different properties, as abusers seek to exploit the unique vulnerabilities of each particular formulation.

Collegium's Petition focuses almost entirely on Xtampza's resistance to physical manipulation and, particularly, particle size reduction. This resistance may be due to the already fine (approximately 300um) size of the waxy beads in Xtampza capsules. Thus, further reduction of the particle size of the beads may be difficult to achieve and/or may have limited impact on the extended release characteristics of the beads. If they find that attempts to further reduce the particle size are too hard or are ineffective for purposes of facilitating abuse of the product, potential abusers may reasonable focus on chemical means of defeating the formulation.

To evaluate susceptibility to chemical manipulation, the ADF Guidance recommends sponsors undertake a comprehensive assessment of the ease of extracting the opioid from intact and manipulated product, considering a variety of commonly available solvents, other solvents with varying characteristics (e.g., pH, polarity, protic vs. aprotic), and the effects of time, temperature, and agitation on extraction.[7] In order to ensure that tests assess the conditions most likely to defeat a formulation, it is essential to

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[5] Butler, S.F. *et al.,* Relative Abuse of Crush-Resistant Prescription Opioid Tablets via Alternative Oral Modes of Administration, Pain Med. 2017;0;1-5, available at: https://academic.oup.com/painmedicine/article/doi/10.1093/pm/pnx151/3940205/Relative-Abuse-of-Crush-Resistant-Prescription.

[6] ADF Guidance, pp. 6-7.

[7] ADF Guidance, p. 7.

also consider the solubility and miscibility of the components of a test formulation – both the active pharmaceutical ingredient and the key inactive components – as a function of temperature in the target solvent system.

Based on the results of these rigorous *in vitro* tests, manipulations that most effectively and most efficiently defeat the formulation should then be used in pharmacokinetic and human abuse potential studies. Specifically, the ADF Guidance instructs sponsors conducting clinical abuse potential studies (Category 3) to manipulate the test and comparator products "based on the results of Category 1 [*in vitro*] studies to cause the highest release of the opioid and the highest plasma levels." Similarly, Category 2 pharmacokinetic studies are to evaluate "the methods explored during in vitro testing that can be expected to result in the greatest drug release."[8]

Collegium's testing of Xtampza violated these important principles.

II. Simple Extraction Of Unmanipulated Xtampza Beads Releases Substantially All Of The Oxycodone Content In As Little As One Minute

The Xtampza formulation comprises several aliphatic/hydrophobic materials. The most abundant release-rate-controlling waxy excipients, *i.e.*, yellow beeswax and carnauba wax,[9] have melting points ranging between 62 and 86°C. In addition, the oxycodone in Xtampza is the myristic acid salt. These attributes, combined with a basic understanding of solubility/miscibility fundamentals, lead to the conclusion that extraction of oxycodone from Xtampza beads would likely be faster and more easily achieved in more hydrophobic/less-polar and acidic solvent systems and at elevated temperatures. The ADF Guidance requires that such likely vulnerabilities be specifically considered to ensure that Category 1 testing includes methods likely to be used by abusers to deliberately overcome the abuse-deterrent properties of a product.[10] Collegium's Category 1 testing appears not to have properly evaluated Xtampza's vulnerabilities to these simple and obvious manipulations.

Purdue sponsored several extraction experiments designed to evaluate these vulnerabilities using readily available ingestible solvents. The independent laboratory DRUGSCAN performed these experiments, the results of which are provided in the

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[8] ADF Guidance, pp. 12, 8.

[9] Prescribing Information For Xtampza (Nov. 2017), at § 11, Description, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208090s004lbl.pdf ("Xtampza Prescribing Information").

[10] ADF Guidance, pp. 6-7

reports attached as Exhibit 1. The data indicate that Xtampza is highly vulnerable to extraction in these ingestible solvents, making it readily susceptible to oral abuse. Several of the tested methods of extraction quickly and efficiently transform unmanipulated Xtampza beads removed from the capsule shell (as permitted in Xtampza labeling)[11] into a readily-abusable immediate release form of oxycodone suitable for oral ingestion *without* the need for special equipment, uncommon solvents, strenuous physical exertion, or any other form of manipulation or treatment.[12]

Tests that result in >80% extraction in 5 minutes or less:

Results	Solvents	Conditions
>99% in 1 minute[13]	100 mL Coca-Cola®	95° C and constant stirring[14]
90.4% in 5 minutes	100 mL 95% Ethanol	60° C and constant stirring
90.8% in 5 minutes	100 mL tea	95° C and constant stirring
87.6% in 5 minutes	30 mL 95% Ethanol	60° C and constant stirring

[11] The DRUGSCAN reports from which these examples are taken are attached collectively hereto as Exhibit 1. All of the tests conducted by DRUGSCAN evaluated extraction of unmanipulated Xtampza beads removed from the capsule shell (hereinafter "capsule contents").

[12] We note that most of the extraction tests of Xtampza conducted by Collegium and described in the Controlled Substances Staff review of NDA 208-090 appear to have been conducted with "crushed" Xtampza beads. *See* Memorandum to Sharon Hertz, M.D. through Michael Klein, PhD., from James M. Tolliver, Ph.D. and Silvia Calderon, Ph.D. (Sept. 9, 2015), pp. 15-18, available at pages 145-207 of pdf https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208090Orig1s000OtherR.pdf ("CSS Memorandum"). The DRUGSAN tests presented in this comment were all conducted with unmanipulated Xtampza beads. The use of "crushed" beads in Collegium's tests may make it appear that the most effective techniques for extracting the drug from Xtampza require crushing as a first step. However, because additional particle size reduction of the Xtampza beads may be neither necessary nor effective in enhancing the ability to extract the oxycodone component from the beads, highly effective extractions are actually much easier to achieve than even the very limited Collegium data suggest.

[13] The experiment extracting Xtampza capsule contents in 100 mL Coca-Cola® at 95° with constant stirring was performed twice. In the first experiment, 101.7% of the oxycodone content was extracted (average of three replicates), and in the second experiment, 99.4% of the oxycodone content was extracted (average of three replicates). *See* Exhibit 1.

[14] The constant stirring condition involved use of a Grant OLS200 shaking water bath at 200 rpm, which offers a reasonable approximation of vigorous manual stirring.

Tests that result in >80% extraction in 30 minutes or less:

Results	Solvents	Conditions
88.2% in 10 minutes	30 mL vodka (40% ethanol)	60° C and constant stirring
86.8% in 10 minutes	30 mL 40% Ethanol	60° C and constant stirring
87.1% in 10 minutes 91.5% in 30 minutes	100 mL 40% Ethanol	60° C and constant stirring
96.9% in 30 minutes	30 mL 95% Ethanol	Initial 60° C and intermittent stirring[15]
88.6% in 30 minutes	100 mL Coca-Cola®	Initial 95° C and intermittent stirring
82.1% in 30 minutes	30 mL 95% Ethanol	Room temperature and intermittent stirring
80.5% in 30 minutes	100 mL 95% Ethanol	Room temperature and constant stirring

The extraction tests submitted in Collegium's NDA appear to have been conducted at room temperature or, at most, 60°C.[16] Although it is not practical to extract in ethanol at higher temperatures, both because it is flammable and because it will quickly evaporate, there is no reason why tests of extraction in other ingestible solvents such as tea or Coca-Cola® should be limited to 60° C when it is just as practical to heat those liquids to boiling or near boiling (100°C). Indeed, for an abuser, heating those liquids to boiling is easier than heating liquids to and maintaining them at 60° C because there is no need to carefully modulate heating or use a thermometer. Moreover, in light of the melting points of the waxy components of the Xtampza beads, testing only to 60° C could not be expected to represent the point at which the abuse-deterrent properties of the beads would be maximally defeated, as called for by the ADF Guidance.[17] As the data

[15] In the intermittent stirring condition, each timepoint (1, 5, 10, and 30 minutes) utilized its own extraction replicate (3 per each of the 4 time periods, resulting in 12 extractions total per solvent/temperature). Each replicate was stirred initially, with additional stirring as follows:

- One-minute solutions were stirred again for 15 seconds starting 15 seconds before the 1-minute timepoint.
- Five-minute solutions were stirred again 15 seconds before the 2.5 and 5-minute timepoints.
- Ten-minute solutions were stirred again 15 seconds before the 5 and 10-minute timepoints.
- Thirty-minute solutions were stirred again 15 seconds before every 5-minute mark (5, 10, 15, 20, 25, and 30-minute timepoints).

[16] CSS Memorandum, pp. 15-18.

[17] ADF Guidance, p. 6.

provided in Exhibit 1 show, with the application of these higher temperatures, the efficiency of the extraction of oxycodone from intact Xtampza beads is significantly enhanced – to the point of extracting more than 99% of the oxycodone into 100 mL of Coca-Cola® in 1 minute and 90% into 100 mL of tea in 5 minutes.[18]

Given the limitations to Collegium's extraction testing and the ease with which Xtampza is transformed (using simple methods that Collegium does not appear to have tested) into an immediate release form of oxycodone that can be orally ingested, there is no basis to conclude that Xtampza is resistant to extraction, much less any basis to believe that Xtampza is more resistant to oral abuse through chemical extraction than OxyContin is through any practical means of manipulation or extraction.

III. Collegium's Pharmacokinetic And Abuse Potential Studies Are Flawed And Do Not Provide Meaningful Data On Susceptibility To Oral Abuse Through Extraction

The Agency's ADF Guidance instructs sponsors conducting Category 2 pharmacokinetic studies and Category 3 clinical abuse potential studies to manipulate the test and comparator products using the method that results in the greatest drug release.[19] The publicly available results from the *in vitro* experiments conducted by Collegium indicate that extraction is an effective manipulation technique for Xtampza.[20] The data provided with this submission confirm this fact. These data show that extraction of unmanipulated Xtampza beads under conditions that take into account the melting point, solubility, and miscibility of the inactive ingredients, as well as the myristic acid salt form of oxycodone, rapidly results in a readily-abusable immediate release form of oxycodone suitable for oral ingestion *without* the need for any pretreatment, physical manipulation, or uncommon or un-ingestible solvents. Thus, per the ADF Guidance,

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[18] These data also call into question Collegium's assessment of vulnerability to intravenous abuse. Specifically, the experiments performed by DRUGSCAN show that the oxycodone content of unmanipulated beads can be easily and substantially extracted into 30 mL of ingestible liquids, including some amenable to injection such as 40% ethanol. In light of this, and the fact that Xtampza does not contain agents that would cause the solution to gel or otherwise impede syringability, further investigation into Xtampza's vulnerabilities by this route of administration is warranted.

[19] ADF Guidance, pp. 12, 8.

[20] The CSS Memorandum reports, for example, "[w]ith the combination of crushing and elevated solvent (ingestible) temperature, some compromise of the controlled release properties for oxycodone of Xtampza ER microspheres was observed. The most efficient means to extract oxycodone from crushed Xtampza ER microspheres was use of either coke or vinegar held at 60°C. With 1 hour of extraction, greater that 80% LC of oxycodone was extracted." CSS Memorandum, p. 3; *see also* p. 17.

extraction of Xtampza capsule contents should have been the manipulation method tested in both the Category 2 pharmacokinetic and Category 3 human abuse potential studies.

Collegium studied a different method of manipulation in its oral abuse potential studies – chewed Xtampza.[21] Similarly, the Category 2 oral pharmacokinetic studies conducted by Collegium also evaluate only particle-size-reduced Xtampza (crushed and chewed).[22] This choice is inconsistent with both the terms and intent of the ADF Guidance. Chewing, crushing, or otherwise attempting to reduce the particle size of the Xtampza capsule contents had already been shown by Collegium to be a relatively ineffective means of defeating the drug's extended release mechanism – specifically, *in vitro* tests had shown that the already-fine waxy beads in Xtampza capsules are not readily susceptible to further particle-size reduction using the manipulation techniques tested by Collegium. Thus, Collegium's choice to test only crushed/chewed Xtampza undermines the utility of the studies to assess the susceptibility of Xtampza to oral abuse.

Because Collegium has not conducted an appropriately designed oral abuse potential study utilizing extracted Xtampza beads – which appears to be the most efficient and effective means of compromising the formulation for that purpose – there is no basis to conclude that Xtampza will deter that form of oral abuse or that simple extraction will not be the preferred manipulation facilitating oral abuse of the product. Collegium's pharmacokinetic studies also provide no meaningful supportive data because those studies similarly failed to evaluate product manipulated using the most efficient and effective means of compromising the formulation for purposes of oral abuse. Certainly, those studies do not establish that Xtampza is a more robust formulation than any other abuse deterrent product, or that Xtampza should be considered a gold standard against which other abuse deterrent formulations should be measured.

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[21] One oral abuse potential study, CP-OXYDET-24, was considered as part of the NDA. The second study was presented at the 2017 PAINWeek conference. *See* (2017) PAINWeek Abstract Book 2017, Postgraduate Medicine, 129:sup1, 1-85, DOI: 10.1080/00325481.2017.1367065, at abstract 19, available at: https://www.tandfonline.com/doi/abs/10.1080/00325481.2017.1367065.

[22] Two pharmacokinetic studies, CP-OXYDET-17 and CP-OXYDET-25, were considered as part of the NDA. A third study was recently published. Brennan, M.J. *et al.*, The comparative pharmacokinetics of physical manipulation by crushing of Xtampza ER compared with OxyContin, Pain Manag. (Epub ahead of print 18 Sept. 2017), available at: https://www.futuremedicine.com/doi/pdf/10.2217/pmt-2017-0030.

IV. The Xtampza Alcohol Interaction Study Is Inadequate to Assess The Risk of Alcohol-Induced Dose Dumping

The DRUGSCAN experiments presented above show that unmanipulated Xtampza beads can be compromised by extraction in ethanol when heated and stirred. These data indicate that there is a risk that the formulation will dose-dump when co-administered with alcohol when the capsule contents are ingested (consistent with label directions) after being removed from the capsule. This risk is implicated by intentional co-administration of Xtampza with alcohol for purposes of abuse, as well as inadvertent co-administration by patients who disregard the warning against taking Xtampza with alcohol.[23]

To further explore the potential for alcohol-induced dose dumping, Purdue sponsored *in vitro* alcohol dissolution studies of intact Xtampza capsules and Xtampza capsule contents in two media – 0.1N HCl and Fed State Simulated Intestinal Fluid ("FeSSIF").[24] Four different alcohol concentrations were tested in each media: 0, 5, 20, and 40%. The independent laboratory Avista Pharma conducted these experiments, the results of which are reported in Exhibit 2. As discussed further below, these data suggest that unmanipulated Xtampza beads may rapidly release oxycodone when the beads are co-administered with alcohol, implicating patient safety as well as susceptibility to oral

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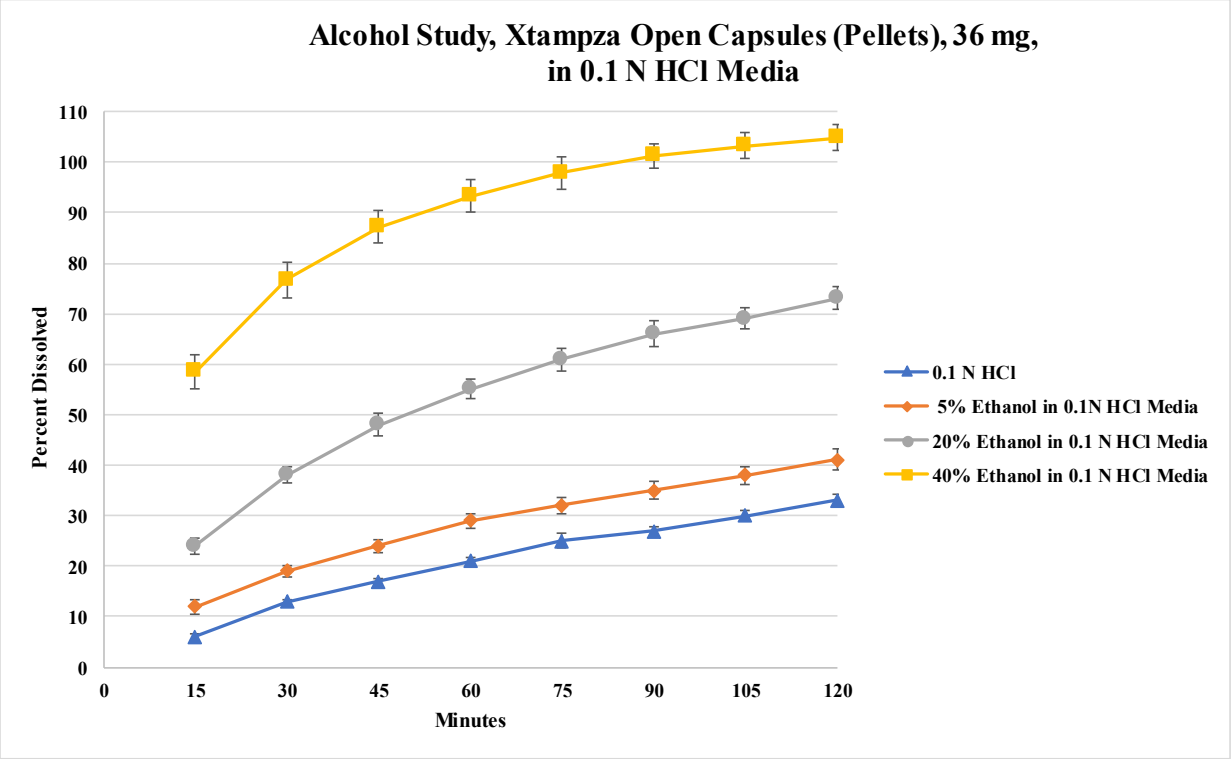
[23] The Agency has acknowledged the potential for patients to disregard the warning against consuming alcohol while taking opioid analgesics. In July 2005, FDA requested that Purdue voluntarily suspend sales and marketing of Palladone® (hydromorphone HCl extended–release) Capsules. FDA's request that Purdue suspend distribution was based on pharmacokinetic data provided to the Agency by Purdue showing that co-ingestion of Palladone with alcohol results in an increase in the peak plasma concentrations of hydromorphone. The labeling for Palladone included strong warnings against co-ingestion of Palladone and alcohol, including a Black Box warning and patient labeling. In addition, in initial distribution, there was no evidence of any such co-ingestion having occurred or having resulted in harm. However, FDA nevertheless believed that some patients may not comply with the warning against co-ingestion of Palladone and alcohol. Therefore, given the potential serious health consequences of opioid overdose, the Agency determined that the overall risk/benefit profile of Palladone, as formulated, was unfavorable and that distribution of the product should be suspended. *See* Information for Healthcare Professionals: Hydromorphone Hydrochloride Extended-Release Capsules (marketed as Palladone), available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129288.htm; Public Health Advisory: Suspended Marketing of Palladone (hydromorphone hydrochloride, extended-release capsules) (7/13/2005), available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051743.htm; Palladone Package Insert and Medication Guide (2004), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/021044lbl.pdf.

[24] 0.1 N HCl is a standard, low-pH aqueous solution that simulates a fasted environment. FeSSIF is dissolution media that simulates the properties of human intestinal fluids following a meal. This latter media is particularly relevant, in that Xtampza is labeled to be taken with food. *See, e.g.,* Xtampza Prescribing Information, §§ 2.1, 2.2, 2.6, 17, Medication Guide.

abuse. Accordingly, these data substantially undermine Collegium's position that Xtampza is safer and/or more resistant to abuse than OxyContin, which has been shown to be resistant to alcohol-induced dose dumping.[25]

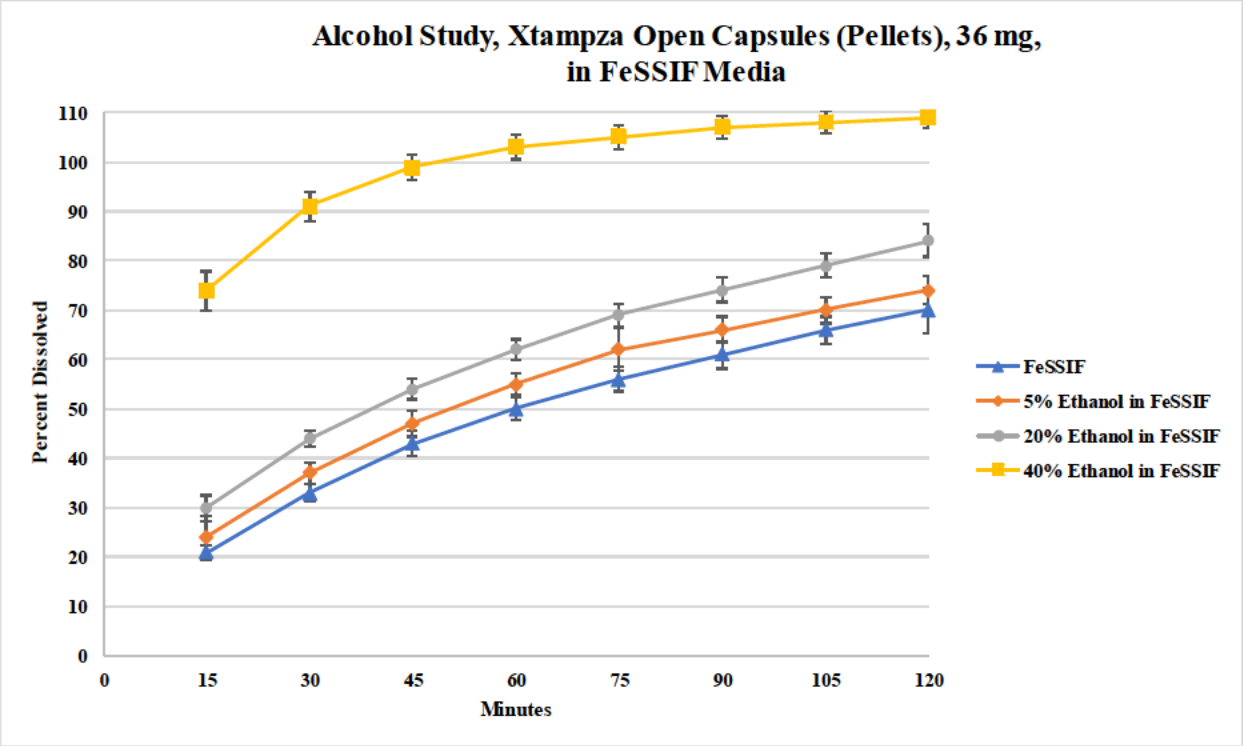
Studies evaluating dissolution of the capsule contents in both media show a trend of increasing rate of release with increasing alcohol content of the media. For instance, by the 15-minute timepoint, a large percentage of the oxycodone content had been released in the 40% ethanol condition; specifically, 58% released in 0.1 N HCl and 74% released in FeSSIF. Over 90% of the oxycodone content was released by the 60-minute timepoint in 0.1 N HCl media and by the 30-minute timepoint in FeSSIF media. Data on all four tested concentrations of alcohol are presented graphically in the figures below, taken from the Avista Pharma report (Exhibit 2):

Figure 2. Alcohol Study, Xtampza Open Capsules (Pellets), 36 mg, in 0.1 N HCl Media



[25] Indeed, dissolution tests data submitted to the OxyContin NDA show that there is an inverse relationship between percent release and ethanol concentration. *See,,* Clinical Pharmacology Review, NDA 22-272, pp. 49-51 of pdf available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022272s000clinpharmr.pdf. ("No dose dumping is expected with OTR formulation.")

Figure 4. Alcohol Study, Xtampza Open Capsules (Pellets), 36 mg, in FeSSIF Media



The intact capsule dissolution rates are less affected by the presence of alcohol. Moreover, in the intact-capsule tests, there was significant variability in both media due to differences in rate of disintegration of the capsule shells and other factors such as the position of the capsule in the basket apparatus.[26] These results are not unexpected, given the composition of the capsule shells – primarily hypromellose ("HPMC"). HPMC has low solubility in alcohol and, therefore, capsule rupture and disintegration times are erratic in media containing alcohol.

These *in vitro* data suggest that unmanipulated Xtampza beads may rapidly release oxycodone when the beads are co-administered with alcohol. Though these data suggest the potential for dangerous release of oxycodone in the presence of alcohol whether or not the beads are ingested with food, it appears the risk is greater if the capsule contents are ingested with food. This finding is notable, as the Xtampza label expressly directs that Xtampza be taken with food.[27]

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[26] Data on the intact capsule testing is depicted graphically in Figures 1 and 3 of the Avista report, Exhibit 2.

[27] *See, e.g.,* Xtampza Prescribing Information, §§ 2.1, 2.2, 2.6, 17, Medication Guide.

Though Collegium conducted *in vivo* alcohol interaction studies, it does not appear the studies were designed to properly evaluate the risk of alcohol-induced dose dumping under relevant conditions. First, there is no indication that the *in vivo* tests of the co-administration of Xtampza capsules with alcohol were conducted using the capsule contents (as opposed to intact capsules). This is an important limitation to the Collegium studies because the capsule shell material (HPMC) is resistant to dissolution in alcohol, while the Xtampza beads are not, due to the different properties of the materials. For this reason, it is relevant and important to evaluate the extraction potential of Xtampza beads alone (*i.e.*, removed from the hard-HPMC capsule, which can be easily done, consistent with the sprinkle administration indication), particularly because the prescribing information provides for administration of the capsule contents sprinkled on soft foods or directly into the mouth, or via a gastrostomy or nasogastric feeding tube.[28]

In addition, it appears that Collegium tested the vulnerability of intact Xtampza capsules to dose dumping when co-administered with alcohol only under fasted conditions,[29] even though release of oxycodone from Xtampza capsules is significantly impaired under fasted conditions, and the approved prescribing information for Xtampza explicitly requires that the drug be taken with food. The *in vivo* alcohol tests conducted by Collegium – which nevertheless show an increased absorption of the drug when co-administered with alcohol in the fasted state – may thus not predict the degree by which absorption would be increased by co-administration with alcohol under fed conditions. As FDA has recognized in the ADF Guidance, such a study would have to be conducted before the degree of risk associated with the interaction between Xtampza and alcohol can even be estimated, let alone concluded to be acceptable.[30]

In summary, to adequately assess the potential impact of co-administration of alcohol on the absorption of Xtampza capsule contents, it would be necessary to conduct well-designed *in vivo* tests. The *in vitro* data provided with this comment indicate that Collegium has not conducted the necessary tests to adequately evaluate the risk of alcohol induced dose dumping with Xtampza. This is a significant weakness that implicates patient safety as well as the potential for oral abuse of Xtampza. It also substantially undercuts the suggestion by Collegium that Xtampza is safer and/or more

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[28] Xtampza Prescribing Information, at §§ 2.1, 2.6, Medication Guide.

[29] Clinical Pharmacology Review, NDA 208090, p. 21 of pdf available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208090Orig1s000ClinPharmR.pdf.

[30] "If food significantly increases systemic exposure of the intact formulation, the underlying mechanism for the food effect should be established by assessing whether the effect is based on the drug substance or the formulation and whether the effect is present with intact product as well as with manipulated product. When food is expected to increase exposure, subsequent abuse potential studies of the oral route should be conducted in the fed state to maximize the potential systemic exposure." ADF Guidance, p. 9.

resistant to abuse than OxyContin, which, as noted above, has been shown to be resistant to alcohol-induced dose dumping.

V. Collegium's Claims Of Superior Resistance To Intranasal Abuse Are Unsupported

In asserting that Xtampza is more resistant to intranasal abuse than OxyContin, Collegium's Petition mischaracterizes the OxyContin intranasal abuse potential study and presents a misleading and scientifically invalid comparison of data from that study and the Xtampza intranasal abuse potential study.

First, Collegium incorrectly states that the primary endpoint of Drug Liking Emax in the OxyContin intranasal abuse potential study (OTR1018) was not statistically significant.[31] In fact, the critical Emax comparisons in OTR1018, including Drug Liking Emax, showed statistically-significant and clinically meaningful reductions in drug-liking for manipulated OxyContin as compared to the positive control treatments (crushed original OxyContin and oxycodone API powder) following nasal insufflation. Purdue proposed inclusion of statements regarding statistical significance and of associated p-values in the labeling for reformulated OxyContin. However, at the time of the labeling approval in April 2013, FDA held the view that such statements should not be included in labeling. The inclusion of statements regarding statistical significance in labeling for some more recently approved abuse deterrent opioids appears to reflect FDA's evolving views on the utility of this information in drug labels.

The statistical analysis results for the drug liking VAS assessments, as reported in the Clinical Study Report for study OTR1018, are presented in the table below. This table presents the descriptive statistics (mean and standard deviation) and the associated p-values for the pairwise treatment comparisons for the Drug Liking VAS Emax endpoint. The differences noted between the treatments in these comparisons were each statistically significant.

[31] Collegium Petition, p. 15.

TABLE: OTR1018 Statistical Analysis Results for Drug Liking Emax

Mean (SD) Drug Liking Emax Analysis				
Test Treatment	**Emax**	**Control Treatment**	**Emax**	**p-value**
OTR_F	80.4 (20.9)	Oxycodone Powder	89.3 (16.6)	0.006
OTR_C	72.7 (22.5)	Oxycodone Powder	89.3 (16.6)	< .001
OTR_F	80.4 (20.9)	Crushed Original OxyContin	94.0 (14.1)	< .001
OTR_C	72.7 (22.5)	Crushed Original OxyContin	94.0 (14.1)	< .001
OTR_F = Finely crushed reformulated OxyContin				
OTR_C = Coarsely crushed reformulated OxyContin				

The publicly available review by FDA's Controlled Substances Staff of Purdue's intranasal abuse potential study states that the results were statistically significant:

> Group statistics and individual responder analysis reveals that the intranasal administration of finely crushed or coarsely crushed 30 mg OTR is generally associated with a **statistically, significantly lower** level of drug liking compared to similar administration of finely crushed 30 mg original Oxycontin or powdered 30 mg Oxycodone HCl API.[32]

The published journal article reporting results of the OxyContin intranasal abuse potential study also states that the results were statistically significant.

> Table 2 presents mean (SD) E_{max} values for Overall Drug Liking VAS, Take Drug Again VAS, and SDV. All active treatments had E_{max} values that were **significantly greater** versus OC placebo ($P \leq .003$) except coarsely crushed ORF, which did not differ from OC placebo on Overall Drug Liking ($P = .07$). Finely and coarsely crushed ORF had **significantly lower** E_{max} values versus positive controls for all three global measures of drug effect ($P \leq .002$).[33]

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[32] Controlled Substances Staff Review, NDA 22-272 (Sept. 21, 2012) (emphasis supplied), p. 288 of pdf available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014OtherR.pdf.

[33] Harris, SC, *et al.,* Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users, J. Clin. Pharmacol. 2014 Apr;54(4):468-77. doi: 10.1002/jcph.235. Epub 2013 Dec 11, at p. 473 (emphasis supplied) (available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4263153/).

Thus, Collegium's assertion that the findings of the human abuse liability study of intranasal abuse of OxyContin were not statistically significant is incorrect.

Collegium also speculates that the OxyContin label does not include data from pharmacokinetic studies of intranasal administration "due to the fact that simple methods of manipulation have been shown to defeat the time release system and cause uncontrolled dose dumping."[34] Collegium is wrong. Purdue originally proposed draft labeling that included Category 2 pharmacokinetic data obtained from its intranasal human abuse potential study (OTR1018). During its review, however, FDA questioned the utility of including Category 2 pharmacokinetic data in the OxyContin label. Ultimately Purdue agreed with FDA to omit Category 2 data in view of the inclusion of the more important claims based on both Category 1 testing and the intranasal human abuse potential study OTR1018.

Moreover, the Category 2 pharmacokinetic data from study OTR1018 do not show "uncontrolled dose dumping." Rather, these data show that both manipulated versions of reformulated OxyContin (fine and coarse particles) produced oxycodone pharmacokinetic profiles following intranasal administration that differed substantially from the pharmacokinetic profiles of the two positive oxycodone controls. The pharmacokinetic profiles for manipulated OxyContin featured peak oxycodone concentrations that were lower and that occurred later, as compared to either of the positive treatments. These findings clearly demonstrate that the oxycodone release control mechanism was not defeated and that uncontrolled dose dumping did not occur even after the manipulations of reformulated OxyContin tablets, both of which required a meaningful degree of time and effort as well as specific equipment.

FDA's publicly available assessment of the Category 2 pharmacokinetic data from study OTR1018 further refutes Collegium's speculation that pharmacokinetic data show uncontrolled dose dumping. The Agency's Controlled Substances Staff described the pharmacokinetic data as follows:

> Overall, the results provided by the Sponsor regarding pharmacokinetic analysis of oxycodone demonstrated that intranasal administration of finely crushed OTR or coarsely crushed OTR resulted in lower oxycodone maximum plasma concentrations (Cmax), greater time to achieve oxycodone Cmax (Tmax) compared to the intranasal application of either finely crushed OxyContin or powdered 30 mg Oxycodone HCl API. Total oxycodone exposure was similar across treatments. The reduction in oxycodone Cmax and increase in oxycodone Tmax, along with no change in total drug exposure, is supportive of a reduced

[34] Collegium Petition, pp. 13-14.

susceptibility to intranasal abuse of 30 mg OTR compared to intranasal abuse of 30 mg original OxyContin or powdered 30 mg Oxycodone HCl API.[35]

The lack of dose dumping is also evident from the pharmacokinetic data presented in the journal article published over four years ago reporting results of the OxyContin intranasal abuse potential study.[36]

Finally, Collegium suggests that Xtampza has greater resistance to intranasal abuse than OxyContin based on a comparison of the data derived from Collegium's intranasal abuse potential study and Purdue's abuse potential study. However, neither study included both products, so there were no head-to-head comparisons.[37] Moreover, the liking data for the positive controls were different between the two studies, as were the doses administered (36 mg crushed Xtampza, equivalent to 40 mg oxycodone HCl vs. 30 mg OxyContin). These and other differences between the studies further undercut the credibility of any attempted cross-study comparisons. In addition, comparisons of data from abuse potential studies of products that use different technological approaches to abuse deterrence are particularly misleading because test product sample preparations differ (or should differ) but, in order to reduce the impact of this variable, are standardized separately for each product and are not undertaken by the study subjects themselves. For all of these reasons, Purdue believes that FDA should reject any cross-study comparisons between Xtampza and OxyContin and acknowledge that such comparisons are unwarranted, as the Agency would ordinarily do for superiority claims in the absence of direct comparisons.

Importantly, even if there were direct, properly controlled and otherwise meaningful head-to-head comparisons, the significance of those comparisons would nevertheless be unclear given the current lack of any quantitative correlation between reductions in measures of drug liking and reductions in rates of abuse. Relatedly, Purdue notes that the extent to which abusers will successfully exploit the vulnerabilities of Xtampza is not yet known, due to its relatively recent launch, limited market penetration, and lack of epidemiologic data. In light of these considerations, even if there were relevant head-to-head study data, it would be inappropriate to conclude that Xtampza is

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[35] Controlled Substances Staff Review, NDA 22-272 (Sept. 21, 2012), p. 289 of pdf available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014OtherR.pdf.

[36] Harris, SC, *et al.,* Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users, J. Clin. Pharmacol. 2014 Apr;54(4):468-77. doi: 10.1002/jcph.235. Epub 2013 Dec 11, at pp. 472-73 (available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4263153/).

[37] Collegium Petition, pp. 15-16.

more (or even comparably) abuse-deterrent than OxyContin through this or any other route of abuse.[38]

In sum, Collegium's assertions about Purdue's intranasal abuse potential study are unsupported and contradicted by publicly available information contained in the Controlled Substances Staff review and the Journal of Clinical Pharmacology article reporting the results of the study. Moreover, Collegium's comparison of the results of its study with those of the Purdue study is scientifically invalid and provides no basis to conclude that Xtampza will be less attractive to abusers than OxyContin in the real world.

VI. Conclusion

For formulations susceptible to dissolution and extraction, particularly those such as Xtampza that contain very fine particles that can be readily dissolved and extracted in their unmanipulated form, evaluation of oral abuse potential cannot credibly be based solely or primarily on studies investigating the ability to chew, crush, or otherwise reduce the particle-size of the dosage form. Instead, to adequately investigate oral abuse deterrence, studies must include a comprehensive battery of dissolution and extraction experiments under various conditions and in a wide range of media. Collegium either has not done such testing or it has omitted reference to it in its Petition. For this and the other reasons outlined above, the relief requested in Collegium's Petition is unsupported and

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[38] Collegium asserts that Purdue's intranasal abuse potential study "does not meet current required standards for an adequate, well-controlled, robust, rugged, and scientifically rigorous study as defined in FDA's Abuse-Deterrence Guidance." (Collegium Petition, p. 21). Other than the unfounded speculation that the study results were not statistically significant and the pharmacokinetic data show dose dumping, Collegium offers nothing in support of this conclusion. While the study was designed and conducted prior to issuance of FDA's draft and final guidance regarding the evaluation and labeling of abuse-deterrent opioids, critical aspects of the study design were informed by input from expert consultants and from FDA staff (Division of Anesthesia, Analgesia, and Addiction Products and the Controlled Substances Staff). FDA's assessment of Purdue's study is summarized in the publicly available review of the 2013 label supplement adding section 9.2 to the OxyContin label: "DAAAP and CSS reviewed the study protocol and results and concluded that the study was properly designed and conducted. The data describe responses that support the conclusions described below." *See* Labeling Review for Regulatory Action, NDA 22-272, S-014, p. 8 of pdf available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014OtherR.pdf.

Relatedly, Collegium also claims that FDA denied abuse-deterrent labeling for reformulated OxyContin until April 2013 (Collegium Petition, p. 21). However, FDA's draft Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling was not published until January 2013. Moreover, Purdue's intranasal abuse potential study was not reported and submitted to FDA until the fall of 2010, after approval of the NDA. FDA's approval of new language describing the abuse-deterrent attributes of OxyContin in April 2013 was a timely action on Purdue's September 2012 supplement proposing that language.

risks misleading the public about the relative benefits and risks of both Xtampza and OxyContin.

Based on current technology, every abuse-deterrent formulation of a drug will have relative strengths and weaknesses across methods of manipulation and routes of abuse. Better performance in a single specific testing scenario, whether *in vivo* or *in vitro*, does not indicate overall superiority. FDA evaluates the abuse-deterrent properties of products based on the totality of the evidence.[39] Likewise, judgments about overall superiority can credibly be based only on a comprehensive assessment of overall profiles as measured in the laboratory, in the clinic, and in the real world. In this regard, there is far too little experience with abuse deterrent formulations in general (and virtually none that we are aware of on Xtampza) to be able to judge whether observed differences between products in any premarket test can predict meaningful differences in the real world.

Importantly, in the case of Xtampza, the data presented with this comment indicate that the formulation has significant vulnerabilities, readily apparent in laboratory tests, that Collegium's Petition fails to acknowledge, let alone address. Therefore, Collegium's request that the Agency establish Xtampza as the status of a "gold" standard for abuse-deterrent oxycodone formulations is unwarranted and potentially detrimental to the public health.

Beyond the flaws in Collegium's claim to be a superior abuse-deterrent formulation, there are patient-safety reasons to deny the requested relief. Collegium seems to assume that if OxyContin is removed from the market, patients will be prescribed Xtampza instead. This is an unrealistic assumption. Xtampza has a food effect and, not only must be taken with food, but must be taken with approximately the same amount of food for every dose in order to ensure consistent plasma levels are achieved.[40] OxyContin, in contrast, has no food effect and may be taken without regard to meals.[41] Some patients taking OxyContin will not be suitable candidates for Xtampza due to the significant dosing limitations associated with the food effect. Some patients who are switched to Xtampza may find it difficult to comply consistently with those dosage recommendations and may have adverse experiences as a result. Some patients may be switched to immediate-release oxycodone or other extended release opioids which lack any of the important safety benefits of abuse-deterrent formulations that FDA has recognized since at least 2013. And all of this disruption and increased risk to patients and others would be based on the risky, and unsupported, assertion that Xtampza

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[39] ADF Guidance, p. 2.

[40] *See, e.g.,* Xtampza Prescribing Information, §§ 2.1, 2.2, 2.6, 17, Medication Guide.

[41] OxyContin Prescribing Information, § 12.3, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022272s034lbl.pdf.

is more resistant to abuse than OxyContin despite the fact that Xtampza's abuse-deterrent properties can be easily defeated.

The public health and safety requires a more cautious and prudent regulatory policy, based on sound and thoughtful science, than is reflected in Collegium's petition. We therefore request that FDA deny the requested relief.

VII. 505(q) Verification

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about

August 25, 2017	DRUGSCAN Reports
April 9, 2018	Collegium Petition
May 7, 2018	Avista Pharma Report

If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Purdue Pharma L.P. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,

Peter R. Mathers
Jennifer A. Davidson
Counsel for Purdue Pharma L.P.

Exhibits

DRUGSCAN Reports	1
Avista Pharma Report	2

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From:	Peter Mathers
To:	Woodcock, Janet; Throckmorton, Douglas C; Hertz, Sharon H; Dickinson, Elizabeth (FDA); Sipes, Grail
Subject:	Comment on Citizen Petition FDA-2018-P-1448
Date:	Tuesday, May 08, 2018 6:49:49 PM
Attachments:	180508 Purdue Comment on Collegium CP - UNREDACTED.pdf 180508 Purdue CP Comment Exhibit 1 - UNREDACTED.pdf 180508 Purdue CP Comment Exhibit 2 - UNREDACTED.pdf

Attached is an un-redacted comment addressing issues raised in a Citizen Petition filed on behalf of Collegium Pharmaceutical, Inc., dated April 9, 2018 and filed in Docket No. FDA-2018-P-1448.

This comment, which is being submitted on behalf of Purdue Pharma L.P., includes test results pertaining to vulnerabilities in the abuse-deterrent properties of Collegium's Xtampza® (extended-release oxycodone capsules) product, which vulnerabilities are not addressed or acknowledged in the Collegium petition. Because of the risk that certain details of the tests described in this comment could provide a "roadmap" for potential abusers to defeat the Xtampza formulation – including the fact that the entire oxycodone content of unmanipulated Xtampza beads can be extracted in one minute in heated Coca-Cola® -- we are not filing this un-redacted version of the comment to the petition docket at regulations.gov. Instead, we are filing a redacted version of the document that omits the details that we believe would provide such a roadmap. We are also initially omitting the attached study reports (Exhibits 1 and 2 to the comment), pending further consideration of whether any portion of those reports should be posted publicly. In that regard, we would welcome any feedback you or others at the agency may provide regarding whether and which portions of the Exhibits should be made publicly available.

We are also providing complete copies of the attached comment (including the Exhibits) to counsel for Collegium.

Please let me know if there are any questions about this submission.

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September 13, 2018

Via e-filing www.regulations.gov

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Proposed Revision to Hydrocodone Bitartrate, Tablet; extended release; oral Product Specific Guidance, Docket No. FDA-2017-D-0369, Comments from Purdue Pharma L. P.

1. Introduction

Enclosed is a proposed revision to the draft product specific guidance document on Hydrocodone Bitartrate, Tablet; extended release; oral (rev. 7/2018).[1] This proposal ("Proposed Revision") was prepared using the current draft product specific guidance ("Current Draft Guidance") and the guidance document – *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products* (Nov. 2017)[2] ("Generic ADF Guidance") as a basis. The rationale for the Proposed Revision is provided below, with particular emphasis on areas in which the recommendations differ from those in the Current Draft Guidance and the Generic ADF Guidance.

2. Bioequivalence

a. Tablet Strength for Bioequivalence Studies

[1] The Proposed Revision is enclosed as Exhibit 1. The current draft is available on FDA's website at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM220198.pdf. A redline comparing the Proposed Revision to the current draft product specific guidance is enclosed as Exhibit 2.

[2] Available at https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf.

The Proposed Revision provides that the fasting and fed bioequivalence studies be conducted using the highest strength (e.g., 120 mg) of the proposed generic product. Several Agency guidance documents recommend use of the highest strength of the test and reference product in both fasted and fed bioequivalence studies in support of ANDAs, including *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (March 2003) and *Guidance for Industry Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*, Draft (December 2013).[3]

Using the highest strength of the proposed generic product to evaluate fasted and fed bioequivalence is particularly important for abuse deterrent products because these formulations often include additional excipients or additional amounts of excipients in order to impart the abuse deterrent properties. Any impact of these additional materials on bioequivalence is more likely to be apparent in the highest strength because the tablets are usually larger than the lower strengths and potentially more susceptible to differences in GI transit between test and reference products and between the fed and fasted state.

Additionally, because bioequivalence studies of hydrocodone bitartrate extended release tablets are conducted under naltrexone blockade, there is not an apparent safety reason to avoid testing the highest planned strength of a proposed generic product.

The Proposed Revision provides for extended dosing of oral naltrexone, with the last 50 mg dose being given 36 hours after dosing of the study drug. This change is recommended for safety reasons because, per section 12.3 of the Prescribing Information, the RLD has a mean Tmax of 14-16 hours, and peak plasma levels of hydrocodone may occur up to 30 hours after a single dose. The naltrexone dosing provided in the Proposed Revision mirrors that used safely in the Purdue pharmacokinetic ("PK") studies of Hysingla ER.

b. Partial AUC Measures

[3] *See* page 16 of guidance, available at: https://www.fda.gov/ohrms/dockets/ac/03/briefing/3995B1_07_GFI-BioAvail-BioEquiv.pdf and page 11 of guidance, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf. *See also* Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies (Dec. 2002), p. 5, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf.

It is essential that any proposed generic to Hysingla ER demonstrate a PK profile consistent with maintaining therapeutic efficacy for the entire 24 hour dosing interval in order to avoid end of dose failure. Hysingla ER was specifically developed to maintain a high plasma concentration of hydrocodone throughout the 24 hour dosing interval. This design results in a relatively late Tmax of 14-16 hours and high plasma concentrations at the end of the dosing interval. Generic versions must have this same profile to ensure therapeutic equivalence. Effectiveness of Hysingla ER over the dosing interval was evaluated in a chronic pain study by assessing "pain right now" 12 h after dosing and immediately prior to the following dose. The "pain right now" scores were similar at the 2 intervals demonstrating effectiveness over the entire 24 hour dosing interval.

In order to ensure that any generic products have an equivalent PK profile to Hysingla throughout the 24 hour dosing period, an additional PK requirement, of an equivalent partial AUC from 12-24 hours, is provided in the Proposed Revision. This concept is described in Section C of the March 2014 Draft Guidance on *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations*. The section on BE Considerations states:

> In some cases, conclusions of BE based on peak drug concentration (Cmax) and area under the plasma concentration time curve (AUC) between the test product and reference product may be insufficient to demonstrate that there is no difference in safety or efficacy if the systemic concentration-time profiles of the test product and reference product are different (e,g., time to reach peak drug concentration (Tmax) is different). For example, differences in the shape of the systemic concentration profile between the test and reference products could imply that the test product may not product the same clinical response as the reference product. In such cases, additional data analysis (e.g., partial AUCs), exposure-response evaluation, or clinical studies may be recommended to evaluate the BE of the two products.[4]

The text quoted above concerns post-approval changes to reformulated NDA products, but reformulations of NDA products and proposed generic products are both developed to be clinically equivalent to the currently marketed reference product. Consequently, the scientific question to be addressed in a bioequivalence study is the same, and the standards required to be achieved to demonstrate bioequivalence for reformulations of NDA products should also apply to proposed generic products. Indeed, an NDA holder also has the

[4] See page 5 of Guidance, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf.

additional data and knowledge from the clinical program to aid in any assessment of equivalence, and so is actually in a more informed position to assess the impact of differences in the shape of the systemic concentration-time profile than an entity developing a generic product.

c. Waiver of Bioequivalence studies

The Current Draft Guidance provides for waiver of in-vivo testing of lower or intermediate strengths if certain compositional requirements are met and acceptable dissolution data are obtained. The Proposed Revision retains this provision for a waiver. However, applying the definition of "proportionally similar" from the guidance, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*, [5] we note that the reference drug Hysingla ER is not proportionally similar among dosage strengths and we do not expect that many generic products will meet this requirement over the entire 20 to 120 mg dosage range either.

Conducting a dose proportionality study or studies connecting all strengths of the proposed generic product to those used in the bioequivalence studies is preferable to relying on in-vitro data and should be required where the compositional and dissolution requirements are not met. The challenge of developing a generic version of Hysingla ER which meets dose proportionality requirements is generally the same as developing the RLD. The developer of the generic product may utilize any technology or formulation approach necessary to meet the overall project goals and are not constrained to the same technology utilized in Hysingla ER. However, even in a case such as Hysingla ER, where all strengths of tablet have the same total weight, all strengths have the same inactive ingredients, and the change in strength is obtained by altering the amounts of inactive ingredients, primarily the rate controlling polymer, in a consistent and systematic way across strengths, Purdue conducted fasted and fed bioavailability studies with the lowest and highest strengths and a fasted dose proportionality study to connect all intermediate strengths. The Proposed Revision does not require the sponsor of the proposed generic product to conduct bioequivalence studies to bracket the range of strengths being filed and therefore, in the event that requirements for proportional similarity are not met, it is essential that a dose proportionality study be conducted. The Proposed Revision allows the sponsor of the proposed generic product to conduct a single dose proportionality study across all strengths or to divide the strengths into multiple studies where one study includes the highest strength (as used in fasted and fed BE studies) and any additional dose proportionality studies connect to the first study by testing at least one common strength.

[5] *See* page 12 of guidance, available at: https://www.fda.gov/ohrms/dockets/ac/03/briefing/3995B1_07_GFI-BioAvail-BioEquiv.pdf.

3. Abuse Deterrence

a. General

As stated in Section II of the Generic ADF Guidance, "marketing a generic version of the RLD that is less abuse deterrent could lead opioid abusers to preferentially seek out and abuse such easier-to-abuse generics" and therefore it is essential that potential generic products are fully evaluated to ensure that they are not less abuse deterrent than the reference product. Section III of the Generic ADF Guidance states that the "applicant should evaluate its proposed generic drug product to show that it is no less abuse deterrent than the RLD with respect to **all** of the potential routes of abuse and minimize the risk of shifting abuse to other, potentially more dangerous routes."[6] Consistent with these principles, the testing recommended in the Proposed Revision for potential generic versions of Hysingla ER is focused on ensuring that such products are not less abuse deterrent than Hysingla ER by any route, and consequently not preferentially sought out by opioid abusers.

The Proposed Revision provides for testing of all strengths of Test ("T") and Reference ("R") products in all in vitro tests. Unlike the Current Draft Guidance, the Proposed Revision does not provide for the option of conducting in-vitro tests only on the highest strength based on compositional proportionality across all proposed strengths of the generic formulation. If all proposed strengths of a generic formulation were compositionally proportional, the 120 mg tablet would contain up to 6x more of the agents included to deter abuse, compared to the lower strength tablets. There is no basis to assume similar abuse deterrence among tablets containing varying amounts of these agents, much less abuse deterrence equivalent to all strengths of the R product. By way of example, viscosity, which is important for resistance to intravenous abuse, increases much more than linearly with increases in concentration and quantity of gelling agent. For this reason, testing only the strength with the most gelling agent and not testing any of the others (which have proportionally less gelling agent) risks missing vulnerabilities presented by the lower strengths. Recognizing that compositional proportionality would not typically be the optimal method of formulating products designed to be abuse deterrent with a 6-fold range of strengths, the R product was designed to exhibit similar abuse deterrence across dosage strengths by use of varying, non-proportional amounts of gelling agent.

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[6] *See* pages 5, 6, of the guidance, available at: https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf.

For proposed generic versions of Hysingla ER, a bracketing design that would limit testing of some of the proposed strengths should only be pursued if discussed and agreed with the Agency. It is important to involve the Agency in development of any proposed bracketing approach because knowledge of differences between strengths of the R product in formulation, and any manufacturing process parameters which contribute to abuse deterrence, is important in determining whether a bracketing design may be appropriate for this comparison, and this information is not publicly available. An appropriate bracketing approach could not be devised by a generic sponsor based solely on its knowledge of the formulations and manufacturing processes employed in the manufacture of the various proposed strengths of the T product. Without knowledge of the specific manner in which the formulation and manufacturing parameters for each of the different strengths of the R product have been optimized, a generic sponsor cannot credibly devise a rationale for an in vitro testing short-cut based on bracketing that will ensure comparability between each strength of the T and the R products. In assessing any bracketing approach, the Agency should take into consideration the composition and manufacturing variations across strengths of the T and R products and ensure not only that the bracketing approach is adequate to characterize all strengths of T, but also that it enable an effective comparison with R.

The Proposed Revision also indicates that applicants should specify and justify the total number of tablet units used in a manipulation run (e.g., milling). The number of tablets used in each individual manipulation is an important consideration that materially impacts the efficiency of the manipulation and the percentage of the total sample that is lost in the process. Depending on the specific manipulation, the number of tablets needed to produce the maximum particle size reduction achievable may differ from the number of tablets needed to produce a consistent sample appropriate for use in subsequent tests. The optimal number of tablets needed for these purposes may be greater than the number reasonably anticipated to be used in real world abuse settings. Sponsors should justify the total number of tablet units used for each manipulation, taking into account the efficiency of the manipulation, the total percentage lost, the purpose of the manipulation, and the need for the particular manipulation to reflect anticipated actual abuse scenarios.

The Proposed Revision also provides for justification of both the tools selected for physical manipulation and the intervals at which each tool is replaced during in-vitro testing. The cutting edges of manually and electronically powered tools can become dull or damaged during attempts at particle size reduction, which will materially alter their ability to perform this function and/or their efficiency in doing so. Similarly, the motors of electronically powered tools may become compromised over time. For these reasons, tools should be replaced at appropriate intervals in order to minimize the impact of these variables.

b. Physical Manipulation and Extractability

Physical Manipulation: Hysingla ER tablets are formulated with inactive ingredients intended to make the tablets more difficult to manipulate for misuse. Hysingla ER is a matrix tablet formulation where all strengths have significant resistance to physical manipulation. Section 9.2 of the label reflects this, stating, "In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that Hysingla ER resists crushing, breaking, and dissolution using a variety of tools….." Moreover, the time and effort required to prepare a product for abuse is thought to affect its attractiveness for abuse[7] and, in the specific case of Hysingla ER, the level of difficulty in achieving particle size reduction was a contributing factor to the product obtaining an oral abuse-deterrence claim. For these reasons, the Proposed Revision reflects that tests of a proposed generic product need to demonstrate at least equivalent resistance to particle size reduction in order to establish that the proposed generic product is no less abuse deterrent than Hysingla ER.

Extractability: The tests recommended in the Proposed Revision are generally in agreement with those described in Appendix 1 of the Generic ADF Guidance. However, we recommend that extraction testing be completed on all Levels of solvents, irrespective of the results obtained during evaluation of reference product, in order to have essential information on the vulnerability of the different products in each solvent and how they compare. By way of example, if only the test sequence specified in the Generic ADF Guidance is applied, a proposed generic product that releases substantially all of its drug content within a few minutes in a "Level 2" solvent might never be tested in that solvent, yet this is an important vulnerability that should be documented and considered by the Agency. These data will also provide information for additional in-vitro studies, such as those to evaluate abuse by injection, as well as important information on potential solvents for oral abuse. Many of the solvents, especially in Level 2, are extremely easy to obtain and extracting the contents of the dosage form into them is similarly attractive to a potential abuser as extracting into the one Level 1 solvent (deionized water). Therefore, conducting the extraction studies using all of the solvents ensures that a thorough evaluation of the proposed generic product is conducted and compared to that of the RLD even if extraction in deionized water under Tier 1 conditions (e.g., in 30 minutes) resulted in extraction of over 50% of the RLD. The Proposed Revision provides for such testing but with slightly different, more flexible, acceptance criteria, allowing a proposed generic to pass extraction testing even if it performs worse than Hysingla ER in a particular solvent, so long as it releases the same or less drug than Hysingla ER under the same test conditions in deionized water.

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[7] *See, e.g.*, Cone, E. *et al.*, The ALERRT ® instrument: a quantitative measure of the effort required to compromise prescription opioid abuse-deterrent tablets, Am. J. Drug Alcoh. Abuse (2017). 43; 3; 291-98, at 292 (available at: https://www.tandfonline.com/doi/pdf/10.1080/00952990.2016.1278006?needAccess=true).

The Generic ADF Guidance does not provide for extraction experiments to be performed with agitation. However, stirring can facilitate compromise through extraction and is not difficult for abusers to do. The Proposed Revision provides for extraction testing at 150 rpm as a means to standardize testing of simulated stirring.

Finally, the Proposed Revision provides for testing in different solvents than the Generic ADF Guidance. The Proposed Revision specifies 95% ethanol (compared to 100% in the Generic ADF Guidance) because the Agency's most recent advice to innovators is to test in 95% ethanol. The Proposed Revision also specifies that the carbonated drink tested should have a pH between 2 and 3 because certain formulations are pH-sensitive and can be anticipated to be more readily compromised in a low pH environment. A pH specification is necessary because "carbonated drink" is too broad a category and can therefore be manipulated by choice of, for instance, seltzer water instead of a low pH cola drink. The Proposed Revision does not recommend testing in acetone, isopropyl alcohol, and 0.1N NaOH, because the solubility of hydrocodone bitartrate in these solvents is known to be low, or in 0.1N HCl, because extraction in acidic media is adequately characterized by the studies using vinegar and the carbonated drink with a pH between 2 and 3.

c. Abuse by Injection (parenteral route)

Abuse by injection is recognized as the route which presents the greatest danger to abusers. For example, in a recent study analyzing data from the RADARS System Poison Center Program, researchers determined while the majority of intentional abuse cases reported to United States poison centers are via the oral route of administration, injection abuse is associated with an over 2.5 times greater risk of death or life-threatening event.[8] Due to these risks, it is imperative that potential generic products have resistance to abuse by this route which is at least equivalent to that of Hysingla ER.

In order to adequately assess whether the proposed generic product is at least as resistant to abuse by injection as Hysingla ER, additional testing beyond that defined in the Generic ADF Guidance is required. The Generic ADF Guidance only requires testing using one needle gauge (21 or finer) and one volume (10 ml), with acceptance criteria being based on the amount extracted at one time-point (30 minutes). This does not fully characterize the

[8] Green, JL *et al.*, Medical outcomes associated with prescription opioid abuse via oral and non-oral routes of administration, Drug Alcohol Dep 175 (2017) 140–145, at Table 4, p. 144, available at: http://www.drugandalcoholdependence.com/article/S0376-8716(17)30138-2/pdf; Abuse-Deterrent Opioids — Evaluation and Labeling (April 2015), pp. 22, 4, available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf.

resistance to abuse by injection of the proposed generic product relative to Hysingla ER or take into consideration any adaptation in methods of preparation which abusers could undertake to exploit any specific deficiencies in a proposed generic product. Accordingly, in order to more fully characterize the proposed generic product, it is necessary to understand the impact of extraction volume, needle gauge, agitation, extraction time, and temperature on performance and how those variables impact performance compared to that of Hysingla ER.[9]

The Proposed Revisions provides for additional testing in smaller volumes (2 and 5 ml), which are more realistic simulations of likely abuser behavior than the single 10 ml volume specified in the Generic ADF Guidance. Many abusers will seek to extract and inject using the smallest volume possible; and given the potentially complex relationship between extraction of the hydrocodone and release and activation of the agents included to deter IV abuse, the comparative results obtained using a single relatively large volume (10 ml) may not necessarily be indicative of the results which will be obtained using smaller volumes preferred by abusers. The addition of 2 ml and 5 ml volumes to the 10 ml proposed in the Generic ADF Guidance enables the impact of volume to be characterized adequately.

Testing in 2 ml is included to represent a small volume preferred by potential abusers. Failing to conduct any comparative testing using a realistic simulation of abuser behavior risks approval of a generic product where a potentially critical vulnerability has not been evaluated. The comparative testing at 5 ml is also required because of the complex relationships between hydration, volume, and viscosity described earlier. The quantitative amounts extractable for IV abuse with intermediate volumes cannot be predicted using data obtained with 10 ml and 2 ml. Testing using 5 ml will enable a more comprehensive characterization of the impact of volume and enable the Agency to assess the impact of progressive increases in volume from the potentially ineffective 2 ml to potentially more effective but not preferred 10 ml.

In addition, the Proposed Revision also recommends testing with a larger bore needle, which is more likely to identify differences between the proposed generic and Hysingla ER, and also simulates abuser behavior in response to difficulty using finer-bore needles. Agitation and thermal pretreatment are also methods known to and used by abusers, and both are likely to be effective on certain formulations, increasing the percentage of drug potentially expelled through a syringe. For this reason, these tests should be conducted on tablets as manufactured and also following thermal pretreatment, with and without agitation. Thermal pretreatment is conducted to evaluate whether it facilitates more efficient extraction and not

[9] *See generally*, Altomare, C. *et al.*, Laboratory-based testing to evaluate abuse-deterrent formulations and satisfy the Food and Drug Administration's recommendation for Category 1 Testing, J. Opioid Manag. 2017 Nov/Dec;13(6):441-448, at pp. 445-46, attached hereto as Exhibit 3.

to enable size reduction as indicated in Appendix 1 of the Generic ADF Guidance. In this case it is therefore appropriate to apply the thermal pretreatment after physical manipulation when such samples are being evaluated. Any other approach would risk failing to identify conditions under which the proposed generic product was more easily prepared for abuse by injection.

It is also necessary to test at more than one time point to adequately evaluate formulations with excipients that may affect extractability over time when hydrated (e.g., gelling agents). Effective extraction in small volumes for IV abuse is a balance between extraction of the drug and release and activation of the agents included to deter IV abuse. For example, in the case of systems containing a gelling agent, the increase in viscosity with longer extraction times may result in significantly less hydrocodone being syringeable after 30 minutes than after shorter timeframes. For these reasons, a second, shorter time point of 5 minutes is added, to address the potential that a single 30 minute test could miss potential vulnerabilities to shorter extraction times. As shorter extraction times are also more likely to be preferred by potential abusers, it is critical that they be evaluated.

The Proposed Revision provides for 2 levels of testing, the first in water and the second in additional solvents. The second level of tests would not be conducted if the data in water indicated the test product was more easily prepared for abuse than Hysingla ER. The Proposed Revision also provides for tighter acceptance criteria than that included in the Generic ADF Guidance. For many of the experiments, we anticipate that significantly less than 10% of the Hysingla ER drug content will be able to be expelled from the needle, and, in many cases, this may be very close to zero. Under these circumstances, using acceptance criteria of R+10% would allow for the proposed generic product to be meaningfully less abuse deterrent by this route than Hysingla ER. The recommendation in the Proposed Revision of R+5% still allows the generic product to be less abuse deterrent than Hysingla ER, but with a margin of difference that does not exceed likely test variability.

d. Abuse by Ingestion (oral route)

<u>In-Vitro</u>

As stated previously, resistance to size reduction is a critical aspect of the resistance to oral abuse of Hysingla ER and therefore any proposed generic product determined not to have equivalent resistance to size reduction should not be considered to have equivalent resistance to oral abuse, irrespective of the outcome of the comparative in-vivo study of chewed products.

<u>In-Vivo</u>

The in-vivo study in the Proposed Revision provides for a study of vigorous chewing conditions, using molars, for three minutes. Additional relevant chewing conditions are left to the discretion of the sponsor, but should be justified. It is necessary to specify in the product specific guidance the maximum duration of chewing to assure the chewing conditions are able to discriminate between test and reference products. For example, if it were permissible for the products to be evaluated after a prolonged attempt at chewing when prolonged chewing is not necessary to compromise the test product, then the evaluation of resistance to chewing will not identify and fail products which can be chewed more easily and/or quickly than Hysingla ER.

The proposed in-vivo study also differs from that in the Current Draft Guidance in terms of the details of the PK parameters to be compared. The relationship between the PK parameters typically measured in bioequivalence studies and the pharmacodynamic ("PD") measures relevant to the resistance to oral abuse are not sufficiently understood for a determination of equivalence of chewed products to be made based on Cmax, AUC, and Tmax. It is therefore essential that the comparison of PK profiles of the chewed proposed generic and chewed Hysingla ER include partial AUCs. These partial AUCs should be statistically compared and not simply reported as supportive data.

The Agency's draft guidance *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*, states, "[t]he time to truncate the partial area should be related to a clinically relevant PD measure."[10] Based on the time to mean Maximum Drug Liking and the other PD and PK data from the in-vivo oral abuse study conducted by Purdue (HYD1013), as well as abusers' desire for rapid onset of euphoria, it is necessary to include a parameter which quantifies plasma concentrations shortly after administration. The Proposed Revision therefore recommends $AUC_{(0\text{-}1.5h)}$ be evaluated for this purpose. The Proposed Revision retains the recommendation in the Current Draft Guidance that $AUC_{(0\text{-}3h)}$ also be evaluated, as this aligns with the median T_{Emax}, for the chewed Hysingla tablets from the oral abuse liability study HYD1013. The Proposed Revision also adds $AUC_{(0\text{-}6h)}$ in place of $AUC_{(0\text{-}4h)}$ in order to ensure the PK comparison includes the plasma concentrations responsible for the higher levels of Drug Liking found in study HYD1013 for the first 6h post dose.

e. Abuse by Insufflation (nasal route)

[10] *See* page 5 of guidance, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf. .

In order to show that the proposed generic product is no less abuse resistant by the insufflation route than Hysingla ER, it is necessary for both in-vitro and in-vivo testing to be conducted.

In Vitro

In-vitro testing should generally be conducted as described in Decision Tree 7 in Appendix 4 of the Generic ADF Guidance. However, it is necessary to specify in the product specific guidance that the manipulation technique used to pulverize the proposed generic product to (1) perform the in-vitro comparison (mass percent of fine particles < 500 microns) and (2) achieve the D10 and D90 limits specified in the Decision Tree for use in in-vivo testing, be the minimum energy technique able to achieve these results. Otherwise, the evaluation of whether the reference product can be pulverized to the required size ranges with an equivalent energy method will not be meaningful. For example, if it were permissible for the test product to be milled with a high energy method when one was not necessary, but such a method was necessary to mill Hysingla ER, then the evaluation will not identify and fail products which can be reduced in particle size more easily than Hysingla ER.

In Vivo

The Proposed Revision includes both PK and PD assessments for resistance to abuse by insufflation because the correlation between pharmacokinetic parameters and pharmacodynamic parameters, such as those included in the prescribing information for Hysingla ER (Drug Liking and Take Drug Again) has not been established. It is currently not possible to accurately predict the PD effects of insufflation from PK data alone. Although the study conducted by Purdue to evaluate PK and PD parameters following insufflation of coarse and fine Hysingla ER powder showed a directional relationship between the PK and PD parameters evaluated, any relationship between PK and PD cannot be extended beyond the specific products tested. This was a comparison where the only variable was the extent of size reduction. Different products will have different masses and different compositions, and potentially other variables which could impact PK and PD assessments independently. In order to make determinations of equivalence of resistance to abuse by insufflation from a PK study alone, it would be necessary to have a satisfactory correlation between PK data and PD measures across all formulations, irrespective of their compositional differences. A sponsor seeking approval of an ANDA must establish that its product satisfies the applicable approval criteria in the Act and FDA's implementing regulations.[11] In order to demonstrate the functional equivalence of the abuse deterrent

[11] 21 C.F.R. §§ 12.87(d), 314.200, 314.94(a), 314.127; 21 U.S.C. §§ 355(j)(2)(A), 355(d).

features of its product, a generic manufacturer must establish that its proffered studies evaluate relevant endpoints that have been validated for that purpose. Because available data do not establish that PK data are predictive of PD measures of abuse potential, PK data cannot be relied upon to evaluate comparative intranasal abuse potential of a proposed generic product and Hysingla ER.

As the proposal is for a study with PD measurements in addition to PK, the naltrexone blockade recommended in the Current Draft Guidance is not included.

Acceptance Criteria:

The recommended PD acceptance criteria is that scores for "Maximum Drug Liking" and "Take Drug Again" (the parameters described in Section 9.2 of the prescribing information for Hysingla ER) be no higher than those for Hysingla ER. Purdue is not aware of any data assessing the clinical significance of differences in measures of either Maximum Drug Liking or Take Drug Again. In the absence of information establishing that performing worse on these parameters has no clinical significance, a proposed generic version of Hysingla ER cannot be determined to be no more vulnerable to abuse than Hysingla ER, as required, unless it performs the same or better than Hysingla ER on these parameters.

The Proposed Revision also recommends that the PK of proposed generic products be compared with Hysingla ER using partial AUC measures as acceptance Criteria and not merely as "supportive data" as recommended in the Current Draft Guidance.

As reflected in the Current Draft Guidance, Cmax and AUC alone do not adequately characterize the PK of a product being abused intranasally, necessitating partial AUC measures. The Agency's guidance *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*, states, "[t]he time to truncate the partial area should be related to a clinically relevant PD measure."[12] Based on the time to mean Maximum Drug Liking and the other PD and PK data from in-vivo insufflation study HYD1014 described above,[13] and abusers' desire for rapid onset of euphoria, it is necessary to include a parameter which quantifies plasma concentrations shortly after administration. The Proposed Revision therefore recommends $AUC_{(0\text{-}1.5h)}$ be compared for this purpose. Based on the results of study HYD1014, this will include the rise in plasma concentration up to approximately the T_{Emax}. The Proposed Revision retains the recommendation in the Current

[12] *See* page 5 of guidance, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf.

[13] *See* n.9 above.

Draft Guidance that $AUC_{(0-3h)}$ also be compared, but replaces the currently recommended $AUC_{(0-4h)}$ with $AUC_{(0-6h)}$. The application of the 95% upper bound confidence intervals to these three AUCs will address (a) the initial rise in plasma concentration after administration, (b) the plasma concentration, and duration of the concentration when Liking is close to Emax, and (c) the drop in plasma concentration after Liking at Emax, ensuring that the duration of the plasma concentrations which caused Likings close to Emax do not persist longer following administration of T than of R.

f. Abuse by Smoking (inhalation route)

We propose that testing be conducted and the results evaluated as described in Appendix 5 of the Generic ADF Guidance; therefore no explanation is required.

4. Dissolution Test Methods and Sampling Times

The Proposed Revision recommends two changes to the dissolution testing specified in the Current Draft Guidance. First, when conducting testing on Hysingla ER, it is necessary to use a spring on the top of the basket in order to stop the tablets from floating and sticking to the underside of the top of the basket; otherwise, testing may produce artificially low values. Similar measures may be required for test products. Second, surfactant should not be used in the ethanolic dissolution media, as it could potentially reduce the impact of the ethanol on excipient solubility and wetting of the dosage form, depending on the formulation selected.

5. Dimensions and Swelling

Sections 5.11, 5.12 of the Prescribing Information for Hysingla ER includes warnings concerning potential difficulty in swallowing and risk of obstruction. The *Guidance For Industry: Size, Shape and Other Physical Attributes of Generic Tablets and Capsules* (June 2015)[14] highlights the potential impact of dosage form size and shape on a patient's ability to swallow a particular drug product. Formulating a product with abuse deterrent properties often requires the inclusion of additional materials or greater quantities of components than would be needed if abuse deterrent properties were not sought. Limits should be placed on the dimensions of proposed generic products relative to Hysingla ER in order to minimize the potential for additional concerns related to swallowing or obstruction. Ideally the proposed generic product should be no larger than the same strength of Hysingla ER in any single dimension. However, the Proposed Revision includes limits taken directly from the *Guidance For Industry: Size, Shape and Other Physical Attributes of Generic Tablets and*

[14] Available at: https://www.fda.gov/downloads/drugs/guidances/ucm377938.pdf.

Capsules, in order to provide developers of generic products a limited scope for the product to be larger than Hysingla ER.

The extent to which swelling of a product has the potential to cause difficulty in swallowing or GI obstruction is a function of the original dimensions and the rate and extent of swelling. Purdue was required to conduct in-vitro swelling studies prior to approval of Hysingla ER in order to characterize the change in tablet size over time, as this was considered important in the context of patients with a narrowed GI lumen as a result of surgery or disease and due to reports of formulations with large amounts of polyethylene oxide sticking to esophageal mucosa. Based on these studies the Agency determined that the rate of increase in size was slow enough not to represent a risk for obstruction while passing into the stomach. These conclusions were for Hysingla ER, a product additionally supported by in-vivo/swallowing information from an extensive clinical program, which will not be the case for a proposed generic. The *Guidance For Industry: Size, Shape and Other Physical Attributes of Generic Tablets and Capsules*, and the Proposed Revision allow a proposed generic to be larger than Hysingla ER, and to have a different rate of swelling. It is therefore important that the evaluation of a proposed generic product include an assessment of swelling and the potential impact on GI transit.

Sincerely,

Laykea Tafesse, Ph.D.
Director, Regulatory Affairs
Purdue Pharma L. P.

Exhibits

Proposed Revision	1
Redline Comparing Current Draft Guidance and Proposed Revision	2
Altomare, C. *et al.,* Laboratory-based testing to evaluate abuse-deterrent formulations and satisfy the Food and Drug Administration's recommendation for Category 1 Testing, J. Opioid Manag. 2017 Nov/Dec;13(6):441-448	3

Contains Nonbinding Recommendations

Draft Guidance on Hydrocodone Bitartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Hydrocodone bitartrate

Dosage Form; Route: Tablet; extended release; oral

Recommended Studies: Two bioequivalence studies (1–2) and two in vivo comparative pharmacokinetic (PK) studies for abuse deterrence assessment (3–4)

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: Naltrexone or other opioid antagonist should be incorporated to block the pharmacodynamic (PD) effects of the opioid. The opioid antagonist should be administered well in advance of opioid dosing to achieve adequate blockade of opioid receptors. The most common approach is to administer 50 mg of naltrexone at the following times: (1) 12 hours prior to dosing; (2) at the time of study drug dosing; and (3) 12 hours after the last dose of study drug. Consult with a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 20 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: See comments in Study 1.

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3. Type of study: Fasting, comparative oral PK study of chewed drug products
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 60 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: See comments in Study 1. Patient-relevant chewing conditions that can discriminate between test and reference products' ability of deterring chewing should be identified. Determine relevant PK parameters including maximum concentration (C_{max}), area-under-the-curve (AUC_{0-t} and $AUC_{0-\infty}$), and time to maximum concentration (T_{max}). Applicants should submit partial AUCs (e.g., $AUC_{0-3\ hours}$ and $AUC_{0-4\ hours}$) as supportive data.

4. Type of study: Fasting, comparative nasal PK study with physically manipulated drug products, consistent with the recommendations in FDA's guidance, "*General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*," for tier 2 evaluation of abuse by insufflation as applicable
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 60 mg
   Subjects: Non-dependent recreational opioid users, general population[1]
   Additional Comments: See all comments in Study 1. Take scientifically appropriate and ethical steps to protect human subjects. This should include ensuring that each subject is not physically dependent on opioids (e.g., through a naloxone challenge test) and has not been seeking or undergoing treatment for abuse of controlled substances such that participating in the study could make them vulnerable to relapse.[2] Also see comments on PK parameters in Study 3. Pulverize test and reference products to a particle size range that is considered safe and tolerable for human insufflation studies. Characterize the formulation recovery, drug content, and particle size distribution of physically manipulated test and reference drug products used in the nasal PK study using validated analytical procedures.

Analytes to measure (in appropriate biological fluid): Hydrocodone in plasma

Bioequivalence based on (90% CI): Hydrocodone
Abuse deterrence based on (upper 95% confidence bound): Hydrocodone

Waiver request of in-vivo testing: 30 mg, 40 mg, 80 mg, 100 mg and 120 mg based on (i) acceptable bioequivalence studies on the 20 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Abuse Deterrence Evaluation: Since the FDA has determined that the reference listed drug (RLD) for hydrocodone bitartrate extended-release tablet (NDA 206627) has properties that are expected to deter abuse (as described in Section 9.2 of the approved Full Prescribing Information), you should refer to the guidance, "*General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*," regarding the studies that should be conducted to demonstrate that the proposed generic product is no less abuse-deterrent than the RLD with respect to all potential routes of abuse. Consistent with the guidance, the potential abbreviated new drug application (ANDA) applicants should consider, among other things, the following:

a) Conducting all in vitro abuse deterrence studies using a bracketing design based on appropriate justification (e.g., extremes of the ratios of opioid to excipients contributing to abuse deterrence) or the highest strength based on compositional proportionality of the proposed generic formulations across all strengths.

[1] This means non-dependent recreational opioid users from the general population who have experience in the use of opioids for non-therapeutic purposes.
[2] For criteria on evaluating substance dependence, refer to, for example, the latest version of *Diagnostic and Statistical Manual of Mental Disorders,* Arlington, VA, American Psychiatric Association.

b) Conducting all in vitro abuse deterrence studies comparing test and reference products using an intermediate manipulation method (e.g., cutting, grating), in addition to "intact and most effectively physically manipulated drug products" as described in the general guidance.
c) Specifying and justifying the total number of tablet units used in a manipulation run (e.g., milling).
d) Determining the drug content in manipulated drug products (e.g., cut, grated, or milled) and quantifying the drug loss in samples prior to evaluating extractability.

Dissolution test method and sampling times:
The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units of the test and reference products. Specifications will be determined upon review of the ANDA.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Alcohol dose dumping studies:
Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP Apparatus I (basket) @100 rpm, with or without alcohol;

Test 1: 12 units tested per the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV.

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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF PENNSYLVANIA

PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC., Plaintiff-Petitioner, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, SCOTT GOTTLIEB, M.D., in his official capacity as the Commissioner of Food and Drugs, and his successors and assigns, and THOMAS E. PRICE, M.D., in his official capacity as the Secretary of the United States Department of Health and Human Services, as well as his successors and assigns, Defendants.	**Civil Action No.**

COMPLAINT FOR WRIT IN THE NATURE OF MANDAMUS RELIEF AND FOR THE ISSUANCE OF A PRELIMINARY INJUNCTION WITH EXPEDITED DISCOVERY AND OTHER EQUITABLE RELIEF

NOW COMES Plaintiff-Petitioner Pharmaceutical Manufacturing Research Services, Inc. ("PMRS"), by and through its attorneys, McCarter & English, LLP, and for its Complaint for Writ in the nature of mandamus relief and for the issuance of a preliminary injunction with expedited discovery and other equitable relief against the United States Food and Drug Administration ("FDA"), Scott Gottlieb, M.D., in his official capacity as the Commissioner of

Food and Drugs and his successors and assigns, and Thomas E. Price, M.D., in his official capacity as the Secretary of the United States Department of Health and Human Services and his successors and assigns, hereby alleges as follows:

INTRODUCTION

1. Plaintiff PMRS brings this action for injunctive and declaratory relief and for a writ in the nature of mandamus due to the failure of the FDA and its Commissioner, Scott Gottlieb, M.D., to respond "promptly" to PMRS's Petition for Stay of Action, as required by the applicable statutory and regulatory authorities.

2. Defendants' failure to provide the required prompt response to PMRS's Petition for Stay of Action violates the Administrative Procedure Act ("APA"), 5 U.S.C. § 702, and the Mandamus Act, 28 U.S.C. § 1361.

3. FDA's unreasonable delay warrants this Court's involvement because it presents serious risks to the health and well-being of the American public in light of the ongoing and devastating opioid epidemic, as well as potentially irreparable economic and competitive harm to PMRS.

4. PMRS seeks an order from this Court compelling FDA to respond to PMRS's urgent Petition for Stay of Action, a Petition that raises pressing public health issues that render further delay by FDA patently unreasonable.

5. That Petition was a timely request that FDA stay the effective date of its approval of Inspirion Delivery Services, LLC's New Drug Application 209777 for a product known as ROXYBOND (oxycodone hydrochloride) tablets, ("ROXYBOND" or "Inspirion NDA"), pending FDA's substantive responses to two pending Citizen Petitions previously submitted by PMRS before FDA's approval of ROXYBOND.

6. PMRS's Citizen Petitions, as well as its public comments at numerous FDA meetings in recent years, highlighted several serious flaws in FDA's process for evaluating and approving opioids and sought to engage FDA in connection with the Agency's role in stemming the opioid epidemic plaguing this nation.

7. PMRS was forced to submit the Petition for Stay to prevent another mislabeled and dangerous opioid from entering the market while FDA considers the life-and-death issues raised in PMRS's various submissions.

8. PMRS submitted the Petition for Stay in accordance with FDA's regulation mandating that such petitions must be submitted within 30 days of an agency's action . 21 C.F.R. § 10.35(b).

9. Those same regulations require a similarly prompt response from FDA. 21 C.F.R. § 10.35(e); Proposed Rule, 40 F.R. 40682 (Sept. 13, 1975)).

10. However, nearly three months after submitting its time-sensitive petition, PMRS still has not received any substantive response and yet another mislabeled and dangerous opioid is poised to enter the market despite the issues and science presented to FDA in PMRS's various submissions.

11. The APA requires federal agencies, like FDA, to conclude all matters presented to them "within a reasonable time" and, more specifically, authorizes reviewing courts to "compel agency action unlawfully withheld or unreasonably delayed." 5 U.S.C. §§ 555(b), 706(1).

12. Under FDA's own regulations, it is required to respond "promptly" to PMRS's Petition for Stay, but it has failed to do so. 21 C.F.R. § 10.35(e).

13. To be clear, PMRS emphasizes that it does *not* request a ruling from this Court dictating what FDA's response should be. PMRS simply requests that this Court exercise the

authority granted to it by the APA and the mandamus statute to compel FDA to provide the response it owes PMRS within 30 days.

14. PMRS also seeks preliminary injunctive relief staying the effective date of the ROXYBOND approval until FDA finally provides a substantive response to PMRS's Petition for Stay.

JURISDICTION AND VENUE

15. This Court has subject matter jurisdiction over this action pursuant to: (a) 28 U.S.C. § 1331 ("[t]he district courts shall have original jurisdiction of all civil actions arising under the Constitution, laws, or treaties of the United States," *i.e.*, federal question jurisdiction); (b) 5 U.S.C. §§ 555(b), 702, 706(1) (judicial review provisions of the APA); and (c) 28 U.S.C. § 1361 ("[t]he district courts shall have original jurisdiction of any action in the nature of mandamus to compel an officer or employee of the United States or any agency thereof to perform a duty owed to the plaintiff.").

16. The declaratory relief requested in this action is authorized by 28 U.S.C. §§ 2201, 2202.

17. Venue is proper in the Eastern District of Pennsylvania pursuant to 28 U.S.C. § 1391(e)(1)(C), because that is the District in which Plaintiff-Petitioner PMRS resides.

PARTIES

18. Plaintiff-Petitioner PMRS is a corporation with headquarters located at 202 Precision Road, Horsham, Pennsylvania 19044.

19. As a world-class supplier of pharmaceutical services, PMRS supports the manufacturing of four FDA-approved drug products, two internationally-approved drug products, and numerous developmental and investigational drugs.

20. Defendant FDA is an agency responsible for, among other duties, protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices.

21. FDA's headquarters are located at 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

22. FDA is headed by Defendant Scott Gottlieb, M.D., Commissioner of Food and Drugs, and operates under authority delegated by Congress and Defendant Thomas E. Price, M.D., Secretary of the U.S. Department of Health and Human Services ("HHS"), a federal agency headquartered in the District of Columbia.

23. Commissioner Gottlieb and Secretary Price, and their respective successors and assigns, are sued in their official capacities as the government officials with ultimate responsibility for the actions and failures to act complained of herein.

FACTUAL BACKGROUND

A. The Opioid Epidemic and Its Impact on the Public Health

24. The United States of America is mired in a catastrophic opioid epidemic. *See* Robert M. Califf, M.D., et al., *A Proactive Response to Prescription Opioid Abuse*, 374 N. Engl. J. Med. 1480, 1483-85 (2016).

25. Statistics compiled by the Centers for Disease Control and Prevention ("CDC") demonstrate that, in 2014 alone, almost 2,000,000 Americans abused or were dependent on prescription opioids and that opioids killed more than 33,000 people in 2015, more than any previous year on record.

26. CDC also reports that the number of opioid-related overdose deaths has quadrupled since 1999 and that 91 Americans die every day from an opioid overdose.

27. The public health crisis caused by the opioid epidemic has led to substantial economic harm as well. For example, in 2013 alone, the opioid epidemic resulted in approximately $78.5 billion in economic costs in the United States. C.S. Florence, et al., *The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States*, L. Med. Care. 2016 Oct. 54(10):901-06.

28. Analysis of opioid-related economic harms at the state level indicates that Pennsylvania ranks among the top 10 states in terms of total health care spending related to opioid abuse, with conservative estimates suggesting that the state spends $847 million per year on these costs—most likely significantly higher when the costs of opioid-abuse-related criminal justice and lost workplace productivity are taken into account. Matrix Global Advisors, *Health Care Costs from Opioid Abuse: A State-by-State Analysis* 2 (Apr. 2015), https://drugfree.org/wp-content/uploads/2015/04/Matrix_OpioidAbuse_040415.pdf (last visited Aug. 2, 2017).

B. Insufficient Data to Support Use of Opioids for Chronic Pain

29. FDA defines chronic pain as "either pain persisting for longer than 1 month beyond resolution of the underlying insult, or pain persisting beyond 3 months." FDA, *Guidance for Industry—Analgesic Indications: Developing Drug and Biological Products*, 2 (Feb. 2014), https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384691.pdf (last visited Aug. 2, 2017).

30. Critically, however, after conducting a comprehensive review of the scientific evidence supporting the effectiveness of long-term opioid therapy for chronic pain, the CDC found that:

> Most placebo-controlled, randomized trials of opioids have lasted 6 weeks or less, and we are aware of no study that has compared opioid therapy with other treatments in terms of long-term (more than 1 year) outcomes related to pain,

> function, or quality of life. The few randomized trials to evaluate opioid efficacy for longer than 6 weeks had consistently poor results.

Thomas R. Frieden & Debra Houry, *Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline*, 374 New Eng. J. Med. 1501, 1501 (2016).

31. Indeed, in its March 2016 *Guideline for Prescribing Opioids for Chronic Pain*, the CDC found that "[t]he evidence reviews forming the basis of this guideline clearly illustrate that there is much yet to be learned about the effectiveness, safety, and economic efficiency of long-term opioid therapy." CDC, *Guideline for Prescribing Opioids for Chronic Pain*, at 34 (2016), https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf (last visited Aug. 2, 2017).

32. Thus, the CDC concluded: "The science of opioids for chronic pain is clear: for the vast majority of patients, the known, serious, and too-often-fatal risks far outweigh the unproven and transient benefits." Frieden & Houry, *Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline*, 374 New Eng. J. Med. at 1503.

33. In response to the CDC's report, FDA has acknowledged that "[a] key lesson learned during the development of the CDC guideline is that there is very little research on the long-term benefits of opioids for treating chronic pain[,]" in contrast to the "growing evidence of harms associated with such use, and of the benefits of other nonopioid treatment alternatives." Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 New Eng. J. Med. at 1484.

34. Further, FDA has acknowledged that the Agency "does its best work when high-quality scientific evidence is available to assess the risks and benefits of intended uses of medical products" but that "[u]nfortunately, the field of chronic pain treatment is strikingly deficient in such evidence." *Id.* at 1484.

35. In stark contradiction to both the CDC's findings and its own public statements, FDA continues to approve new opioid products intended for the treatment of chronic pain.

C. PMRS's Identification of Systemic Flaws in FDA's Process for Reviewing and Approving Opioids

36. PMRS's own research and development has revealed systemic flaws with FDA's review and approval of opioids that are undermining FDA's ability to protect the public health and welfare in the face of the opioid-addiction epidemic.

37. Pursuant to 21 C.F.R. §§ 10.20 and 10.30, PMRS raised those critical issues with FDA via Citizen Petitions dated February 19, 2016, and March 6, 2017. Save for a form letter providing an "interim response" to its February 19, 2016, Citizen Petition, however, PMRS has received no substantive response from FDA.[1]

(1) *PMRS's February 2016 Citizen Petition*

38. On February 19, 2016, PMRS submitted a citizen petition to FDA directed at the issue of abuse-deterrent labeling ("February 2016 Citizen Petition"), now pending under Docket No. FDA-2016-P-0645, requesting, in part, that FDA take certain actions, summarized as follows:

a. Apply the existing standards for laboratory-based in vitro manipulation and extraction studies, including both small and large volume extraction, before permitting opioid drug products with potentially abuse-deterrent properties to be approved;

b. Remove Category 3 human abuse-deterrent (liking) studies from the FDA Guidance, "Abuse-Deterrent Opioids Evaluation and Labeling Guidance for Industry" (April 2015), and as a requirement for approval of drug products with

[1] PMRS's Citizen Petitions are pending under docket numbers FDA-2016-P-0645 and FDA-2017-P-1359. PMRS does not seek court intervention at this time in respect of those pending Citizen Petitions, but both petitions provide necessary context regarding the critical issues addressed in PMRS's Petition to Stay Action, which is the subject of this suit, and therefore are discussed in this Section of the Complaint.

potentially abuse deterrent properties as inherently flawed, subjective, and highly prone to manipulation; and

c. Require post-marketing empirical proof through epidemiological or other scientifically rigorous studies that shows that opioid drug products with potential abuse deterrent properties do in fact result in a *meaningful* reduction in misuse, abuse, addiction, overdose and/or death before approving abuse deterrent labeling for opioid drug products and before permitting opioid drug products to be marketed as abuse deterrent.

39. PMRS's February 2016 Citizen Petition also requested that all opioid drug products currently labeled with abuse-deterrent claims be required to meet all three of the requirements specified above or have their abuse-deterrent labeling removed within a reasonable period of time not to exceed six months.[2]

(2) *PMRS's March 2017 Citizen Petition*

40. On March 6, 2017, PMRS submitted a citizen petition to FDA directed at the issue of chronic-use labeling, now pending under Docket No. FDA-2017-P-1359 ("March 2017 Citizen Petition"), requesting, in part, the revocation of all immediate-release ("IR") opioid drug product labeling that "support[s] use for the treatment of chronic pain." PMRS further requested that all IR opioid drug product labeling state that the indication is for "acute pain for a limited duration."

(3) *FDA's Failure to Respond Substantively to PMRS's Citizen Petitions*

41. PMRS has raised the above-discussed issues directly with FDA on multiple occasions, publicly advocating for the agency to reassess its approach to approving opioid products.

[2] In addition, the February 2016 Petition included a request for actions pertaining to OXYCONTIN specifically. (February 2016 Petition, No. FDA-2016-P-0645 at 4.) The OXYCONTIN-specific requests are not addressed in this action.

42. In addition to its two Citizen Petitions, PMRS also has participated in numerous FDA Advisory Committee meetings and public workshops. *See generally* PMRS's comments at the advisory committee meetings pertaining to VANTRELA ER (Jun. 7, 2016), TROXYCA ER (Jun. 8, 2016), ARYMO ER (Aug. 4, 2016), the use of opioids in pediatric patients (Sep. 16, 2016), OPANA ER (Mar. 14, 2017), ROXYBOND (Apr. 5, 2017), and REXISTA (Jul. 26, 2017), as well as the public meeting on premarket evaluation of abuse-deterrent properties (Nov. 1, 2016).

43. To date, however, PMRS has received no substantive response to its Citizen Petitions, no substantive information, and no substantive rationale for FDA's continuation of a seemingly status quo approach that permits flooding the market with opioids labeled as abuse-deterrent and appropriate for chronic use, despite the absence of sufficient data to support those claims.

D. PMRS's May 11, 2017 Petition for Stay of Action

44. Notwithstanding the significant public-health issues discussed in PMRS's various submissions, and notwithstanding FDA's acknowledgment of CDC findings confirming the lack of sufficient data to support use of opioids to treat chronic pain, on April 20, 2017, FDA approved the Inspirion NDA.

45. FDA's treatment of the Inspirion NDA creates a rigid and harmful dichotomy, wherein FDA delays responding substantively to PMRS's Citizen Petitions that raise fundamental questions about FDA's role in facilitating the opioid epidemic, but then rushes to approve yet another opioid product with chronic use labeling and purported abuse-deterrent properties, despite the scientific community's recognition that the evidence needed to support such claims is lacking.

46. On May 11, 2017, and within the 30-day window mandated by FDA, PMRS filed a Petition for Stay of Action ("PSA") pursuant to 21 C.F.R. § 10.35, requesting that FDA stay the effective approval date of ROXYBOND until such time as FDA provides substantive responses to PMRS's Citizen Petitions raising serious safety issues concerning opioids, like ROXYBOND, that are approved for chronic use and/or as abuse-deterrent.

47. After 30 days passed with no response from FDA, PMRS sent Commissioner Gottlieb a letter to ensure his awareness of the PSA and to reiterate the urgency of PMRS's PSA.

48. To date, however, FDA has not provided any response to PMRS's Petition for Stay of Action, except for a two-paragraph letter acknowledging receipt of the PSA but providing no information concerning the time period in which PMRS could expect a response. Months have now passed, opioid addiction rates are climbing, and people continue to die.

49. FDA's continued delay is unreasonable and warrants this Court's intervention to compel a substantive response to the PSA by a date certain.

CLAIM FOR RELIEF

50. The foregoing allegations are incorporated by reference and repeated as though set forth in full herein.

51. PMRS submitted a timely PSA to FDA on May 11, 2017, requesting a stay of the effective approval date of ROXYBOND until FDA provides a substantive response to PMRS's two pending Citizen Petitions.

52. The Administrative Procedure Act requires FDA to respond to PMRS's Petition for Stay of Action "[w]ith due regard for the convenience and necessity of the parties . . . and within a reasonable time." 5 U.S.C. § 555(b).

53. Moreover, the submission of PMRS's PSA imposed a mandatory, non-discretionary duty on Defendant Scott Gottlieb, M.D., Commissioner of Food and Drugs, to review and respond to the Petition "promptly" and with the same type of diligence with which PMRS acted when submitting the Petition for Stay within 30 days of the FDA action at issue. 21 C.F.R. § 10.35(e); Proposed Rule, 40 F.R. 40682 (Sept. 13, 1975).

54. Despite the passage of nearly three months and the urgency presented by the opioid epidemic plaguing the nation, Defendants have failed to provide any substantive response to PMRS's PSA.

55. Requiring PMRS to wait any longer for a response to its Petition before seeking judicial intervention to compel the unreasonably delayed response would be unjust, wasteful, and significantly harmful to the public health, because absent the stay sought by PMRS, Inspirion is free to market another mislabeled and dangerous opioid.

56. Defendants' failure to respond to PMRS's PSA represents "agency action" that has been "unreasonably delayed," and therefore PMRS is entitled to an order from this Court pursuant to the APA and in the nature of mandamus compelling Defendants to provide a substantive response to the pending PSA within 30 days. 5 U.S.C. § 706(1); 28 U.S.C. § 1361.

57. Moreover, PMRS has experienced harm and will experience irreparable harm if ROXYBOND is permitted to launch before FDA decides PMRS's PSA.

58. The critical importance of being first to market is well-established in the pharmaceutical industry.

59. Companies spend considerable research seeking to increase the odds of beating their competitors to market because of the significant commercial disadvantage to missing first approval.

60. In the industry, every month of lead time ahead of a competitor is significant.

61. First-approved and first-moved products are able to establish themselves with physicians and patients in a way that cannot be changed after the fact.

62. FDA's failure to act promptly on PMRS's PSA, therefore, is causing substantial and irreparable harm to PMRS.

WHEREFORE, Plaintiff-Petitioner PMRS prays that this Court enter an Order:

a. Declaring that Defendants have unreasonably delayed in responding to PMRS's PSA submitted on May 11, 2017, and that such unreasonable delay is a violation of the Administrative Procedure Act and applicable FDA regulations;

b. Compelling Defendants, by injunction and/or writ in the nature of mandamus, to provide a substantive response to PMRS's PSA within 30 days of the entry of this Court's Order;

c. Preliminarily staying the effective date of Inspirion Delivery Services, LLC's New Drug Application 209777 for ROXYBOND (oxycodone hydrochloride) tablets until Defendants issue a substantive response to PMRS's PSA; and

d. Awarding PMRS attorneys' fees, reasonable expenses incurred in connection with this action, and such other relief as this Court deems equitable, just, and proper under the circumstances.

McCARTER & ENGLISH, LLP
Attorneys for Plaintiff-Petitioner,
Pharmaceutical Manufacturing Research Services, Inc.

Dated: August 4, 2017

By: _____
Natalie S. Watson
A Member of the Firm
Pennsylvania Attorney ID # 322345

From:	Fanelli, Richard
To:	Hertz, Sharon H
Cc:	Throckmorton, Douglas C; Dickinson, Elizabeth (FDA); Uhl, Kathleen (CDER); Lionberger, Robert
Subject:	Product specific guidance for Hydrocodone Bitartrate ER tablets
Date:	Friday, September 14, 2018 1:07:48 PM
Attachments:	Hydrocodone bitartrate ER tablets Justification for product specific guidance.pdf Hydrocodone bitartrate_oral ER tablet_NDA 206627_RV07-18.pdf Revised Hydrocodone bitartrate_oral ER tablet_NDA 206627_RV07-18.pdf Redline comparing Proposed revision to draft product specific guidance for Hydrocodone bitartrate_oral ER tablet_NDA 206627_RV07-18.pdf

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Dear Dr. Hertz –

Attached is a copy of a comment submitted to the docket yesterday (Docket No. FDA-2017-D-0369) on behalf of Purdue regarding the product-specific bioequivalence guidance for Hysingla ER (hydrocodone bitartrate) extended-release tablets (comment attached along with Current Draft Guidance, the Proposed Revision, and a track-changes version comparing the two versions). Based on review of the November 2017 Guidance for Industry – General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Dosage Form Drug Products, and on our own experience with evaluation of the abuse deterrence of extended release hydrocodone tablets, Purdue's comments suggest a revision of the product-specific guidance for Hysingla ER Tablets. The suggested revision would expand the guidance to include specific test requirements and evaluation criteria applicable to assure that proposed generic versions of Hysingla ER demonstrate a level of abuse deterrence at least as great as Hysingla ER.

With best regards,

Rich

Richard J. Fanelli, Ph.D.
Head of Regulatory Affairs
Purdue Pharma L.P.
Tel: (203) 588-8365
Cell: (203) 496-7204
email: richard.fanelli@pharma.com

From: Kracov, Daniel A.
To: Dickinson, Elizabeth (FDA); Dettelbach, Kim
Subject: RE: Call Tomorrow
Date: Tuesday, August 08, 2017 12:03:15 PM
Attachments: PMRS v. FDA - Complaint (8.4.17)(E.D. Pa.).pdf

After our call today, would you mind if I called to touch base on this newly filed complaint? As you know, we represent Daiichi, the licensee of RoxyBond. Thanks, Dan

Daniel A. Kracov
Partner
Arnold & Porter Kaye Scholer LLP
601 Massachusetts Avenue, NW
Washington, DC 20001
Office: 1-202-942-5120
Facsimile: 1-202-942-5999
daniel.kracov@apks.com

From: Dickinson, Elizabeth (FDA) [mailto:Elizabeth.Dickinson@fda.hhs.gov]
Sent: Monday, August 07, 2017 3:40 PM
To: Kracov, Daniel A.; Dettelbach, Kim
Subject: RE: Call Tomorrow

Thanks, Dan.
Liz

From: Kracov, Daniel A. [mailto:Daniel.Kracov@apks.com]
Sent: Monday, August 07, 2017 12:20 PM
To: Dickinson, Elizabeth (FDA); Dettelbach, Kim
Subject: Call Tomorrow

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(b) (5), (b) (4)

Thanks,
Dan

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http://www.apks.com

From: Kracov, Daniel A.
To: Dickinson, Elizabeth (FDA)
Cc: Dettelbach, Kim; Hutchinson, Shoshana
Subject: RE: Call Tomorrow
Date: Tuesday, August 08, 2017 1:39:26 PM

Will do. Thank you.

Daniel A. Kracov
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From: Dickinson, Elizabeth (FDA) [mailto:Elizabeth.Dickinson@fda.hhs.gov]
Sent: Tuesday, August 08, 2017 1:36 PM
To: Kracov, Daniel A.
Cc: Dettelbach, Kim; Hutchinson, Shoshana
Subject: FW: Call Tomorrow

Dan,

I suggest you speak with Shoshana Hutchinson (copied) about the PMRS case. She is handling it for OCC.

Liz

From: Kracov, Daniel A. [mailto:Daniel.Kracov@apks.com]
Sent: Tuesday, August 08, 2017 12:02 PM
To: Dickinson, Elizabeth (FDA); Dettelbach, Kim
Subject: RE: Call Tomorrow

After our call today, would you mind if I called to touch base on this newly filed complaint? As you know, we represent Daiichi, the licensee of RoxyBond. Thanks, Dan

---

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Partner
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Sent: Monday, August 07, 2017 3:40 PM
To: Kracov, Daniel A.; Dettelbach, Kim
Subject: RE: Call Tomorrow

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Liz

From: Kracov, Daniel A. [mailto:Daniel.Kracov@apks.com]
Sent: Monday, August 07, 2017 12:20 PM
To: Dickinson, Elizabeth (FDA); Dettelbach, Kim
Subject: Call Tomorrow

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(b) (5), (b) (4)

Thanks,

Dan

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http://www.apks.com

Contains Nonbinding Recommendations

Draft Guidance on Oxycodone ~~HCl~~Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic It does not establish any rights for any person and is not binding on FDA or the public You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations To discuss an alternative approach, contact the Office of Generic Drugs

~~This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.~~

Active Ingredient: Oxycodone ~~Hydrochloride~~hydrochloride

Dosage Form; Route: ~~Tablet,~~ Extended ~~Release; Oral~~release tablet; oral

Bioequivalence

Recommended Studies: Two ~~bioequivalence studies (1-2) and one in vivo abuse deterrence~~Studies

~~study (3)~~

1. Type of study: Fasting

Design: Single-dose, two-~~treatment, two-period~~way crossover in-vivo

Strength: ~~40~~80 mg*

Subjects: ~~Males~~Healthy males and ~~non-pregnant, non-lactating~~nonpregnant females, general population.

Additional Comments: ~~Naltrexone or other opioid antagonist~~ A naltrexone blockade should be ~~incorporated~~used to ~~block~~reduce the ~~pharmacodynamic (PD) effects~~risk of ~~the opioid. The opioid antagonist should be administered well in advance~~any opioid-related adverse events. Administration of ~~opioid dosing to achieve adequate blockade of opioid receptors. The most common approach is to administer~~ 50 mg of naltrexone at the following times: (1) 12 hours prior to dosing; (2) at the time of ~~study drug~~ dosing; and (3) 12 hours after the last dose of ~~study~~ drug~~. Consult~~ product. Please consult with a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.

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*If an 80 mg tablet is not intended to be filed, use the highest dosage strength that will be filed.

Recommended Jul 2010; Revised Oct 2016; Jul 2018

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2. Type of study: -Fed

Design: -Single-dose, two-treatment, two-periodway crossover in--vivo

Strength: 4080 mg*

Subjects: MalesHealthy males and non-pregnant, non-lactatingnonpregnant females, general population–.

Additional Comments: Please see the comments: See comments in Study 1 above.

---

3. Type of study: -Fasting, comparative nasal pharmacokinetic (PK) and pharmacodynamic (PD) study with physically manipulated drug products, consistent with the recommendations in FDA's guidance, "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products," for tier 2 evaluation of abuse by insufflation as applicable

Design: -Single-dose, two-treatment, two-period crossover in vivo

Strength: 30 mg

Subjects: -Non-dependent recreational opioid users, general population[1].[1]

Additional comments: See comments in Study 1. Take scientifically appropriate and ethical steps to protect human subjects. This should include ensuring that each subject is

[1] This means non-dependent recreational opioid users from the general population who have experience in the use of opioids for non-therapeutic purposes

[1] This means non-dependent recreational opioid users from the general population who have experience in the use of opioids for non-therapeutic purposes.

Recommended Jul 2010; Revised Oct 2016; Jul 2018

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not physically dependent on opioids (e.g., through a naloxone challenge test) and has not been seeking or undergoing treatment for abuse of controlled substances such that participating in the study could make them vulnerable to relapse.[2] Pulverize test ("T") and reference ("R") products to a particle size range that is considered safe and tolerable for human insufflation studies. Characterize the formulation recovery, drug content, and particle size distribution of physically manipulated ~~test~~T and ~~reference~~R drug products used in the nasal PK study using validated analytical procedures. Determine relevant PK parameters including maximum concentration (Cmax), area-under-the-curve (AUC0-t, and AUC0-∞), partial-area-under-the-curve ($AUC_{(0\text{-}1\ 5h)}$ and $AUC_{(0\text{-}3h)}$), and time to maximum concentration (Tmax). ~~Applicants should submit partial AUCs (e.g., $AUC_{0\ 3\ hours}$ and $AUC_{0\ 4\ hours}$) as supporting data.~~ Determine relevant PD parameters on a VAS bipolar scale including "Drug Liking" and "Take Drug Again." Details of PD study to be agreed with the agency prior to conducting study.

Analytes to measure (in appropriate biological fluid): ~~Oxycodone~~oxycodone in plasma

Bioequivalence based on (90% CI): ~~Oxycodone~~ oxycodone

Abuse deterrence PK based on (upper 95% confidence bound): Oxycodone

Abuse deterrence PD: Emax (maximum Drug Liking) and Take Drug Again no higher than R product.

Waiver request of in-vivo testing: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 60 mg ~~and 80 mg~~(if being filed) based on (i) acceptable bioequivalence studies on the ~~40 mg~~highest strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. If either (ii) or (iii) are not met then the fourth study must be completed.

4. Type of study: Fasted dose Proportionality

Design: Single-dose, crossover in-vivo

Strengths: All

Subjects: Healthy males and nonpregnant females, general population.

---

[2] For criteria on evaluating substance dependence, refer to, for example, the latest version of Diagnostic and Statistical Manual of Mental Disorders, Arlington, VA, American Psychiatric Association.

Additional Comments: Please see the comments on naltrexone blockade for studies 1 and 2 above. The dose proportionality study may be performed as a single study or divided into multiple studies where the studies are connected by a common strength.

Abuse Deterrence ~~Evaluation~~

Evaluating the Abuse-Deterrence: Since the FDA has determined that the ~~RLD~~reference listed drug for oxycodone hydrochloride extended- release tablet ~~(NDA 022272)~~ has abuse-deterrent properties ~~that are expected to deter abuse~~ (as described in ~~Section~~section 9.2 of the approved Full Prescribing Information), ~~you~~the sponsor of a proposed generic version is required to conduct testing to demonstrate that the proposed generic product is no less abuse-deterrent than the reference listed drug with respect to all potential routes of abuse. The sponsor of a proposed generic version of the reference listed drug should refer to the guidance~~,"~~ for industry *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*~~," regarding the studies that should be conducted to demonstrate that the proposed generic product is no less abuse-deterrent than the RLD with respect to all potential routes of abuse.~~ for general information. Consistent with the guidance, the potential ANDA applicants should consider, among other things, the following:

~~(a) Conducting all in vitro abuse deterrence studies using a bracketing design based on appropriate justification (e.g., extremes of the ratios of opioid to excipients contributing to abuse deterrence) or the highest strength based on compositional proportionality of the proposed generic formulations across all strengths.~~

(a) Testing all strengths of T and R products in all in-vitro tests. Alternatively, if the applicant wishes to use a bracketing design, the proposed design and justification should be discussed with the Agency.

(b) Specifying and justifying the total number of tablet units used in ~~a~~each manipulation run (e.g., milling). Justification should address the efficiency of the manipulation, the total percentage lost, the purpose of the manipulation, and the need for the particular manipulation to reflect anticipated actual abuse scenarios.

(c) Specifying and justifying the tools used for physical manipulation and the intervals at which each is replaced during in vitro testing.

(d) Determining the drug content in manipulated drug products (e.g. cut, grated or milled) and quantifying the drug loss in samples prior to evaluating extractability.

Number of replicates: Minimum 3 per in-vitro test.

Physical Manipulation and Extractability

Physical Manipulation:

Determine the most effective method for particle size reduction of T and R products. Manipulation techniques evaluated must be determined based on the properties of the T and R products, taking into account their formulation designs. This evaluation should include at a minimum: mortar and pestle, cutting, grating, and use of an electronic mill.

Compare the time, difficulty, and particle size distribution achieved with each technique.

Acceptance criteria: Effective particle size reduction of T product cannot be possible using a lower energy particle size reduction method than necessary to achieve comparable particle size reduction of the R product in less than five minutes (e.g., a T product that can be effectively manipulated with a mortar and pestle fails).

Extractablity:

Conduct extractability tests on T and R products using the methods detailed in Appendix 1 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*. Conduct testing on intact and physically manipulated T and R products, with shaking at a minimum of 150 rpm in 240 ml of solvent, and evaluate the results in accordance with Appendix 1 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*.

Solvents (minimum): Test the following solvents regardless of the percent of opioid drug substance extracted from R product at 30 minutes: deionized water, commercially available food grade vinegar, carbonated drink (pH 2-3), 0.2% baking soda solution, 40% and 95% ethanol, plus any readily available ingestible solvents anticipated to be more effective than those listed above in defeating T product, based on the formulation and properties of T product.

Temperature: RT and ET (boiling temperature of solvents used)

Acceptance criteria: Mean % released from intact and manipulated T product must be less than or equal to mean % released from intact and manipulated R product in same solvent, or in water + 10%, respectively.

Abuse by Injection (parenteral route)

For T and R products, test: Intact tablets with no thermal pretreatment and with thermal pretreatment and physically manipulated products with no thermal pretreatment and with thermal pretreatment.

Physical Manipulation: Prepare physically manipulated products for in vitro IV abuse deterrence studies using the most effective physical manipulation method and an intermediate manipulation method (e.g., cutting, grating).

Thermal pretreatment: For thermal pretreatment of tablets and ~~optimally~~ physically manipulated materials, pretreatment conditions should be selected based on the time and temperature combination anticipated to maximally increase extraction without causing significant degradation. Optimal time and duration of thermal pretreatment may be different for T and R products and for intact and physically manipulated products. For physically manipulated samples, the thermal pretreatment is applied after physical manipulation.

Solvents: Tier 1: Deionized Water. Tier 2: 40% and 95% ethanol, plus any solvents anticipated to be effective in defeating T product, based on the formulation and properties of T product. Solvents tested must include food grade vinegar and 0.2% baking soda if T product has a pH mediated controlled-release mechanism.

Temperature: RT and ET (boiling temperature of solvents used)

Volume: 2 ml, 5 ml, 10 ml

Needle: 18G, 27G

Extraction Times: Intact 30 mins; Manipulated 5 mins, 30 mins.

Agitation: Shaking (200 rpm), no agitation.

Additional Comments: Determine drug content of the liquid drawn into a syringe and expelled through the needle.

Acceptance criteria – Mean % expelled from T must be less than or equal to mean % expelled from R in same solvent or in in Deionized Water + 5%, respectively. Applied to all test conditions and times. Only required to Test Tier 2 if T passes Tier 1.

Abuse by Insufflation (nasal route)
In-vitro:

Follow Decision Tree 7 in Appendix 4 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*.

The manipulation condition used to pulverize the T product into particles of the required size range for comparison with R must be the minimum energy method able to achieve this. If this is a lower energy method than needed to achieve the same results for R, then T fails the test.

In-vivo:

Refer to Study 3 above.

Abuse by Smoking (inhalation route)

Follow Appendix 5 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*.

Dissolution test method and sampling times:
The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

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[a] For criteria on evaluating substance dependence, refer to, for example, the latest version of *Diagnostic and Statistical Manual of Mental Disorders*, Arlington, VA, American Psychiatric Association

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In addition to the method above, for modified release products, dissolution profiles on 12 dosage units of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5~~,~~ and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. ~~Include~~For reference product, it is necessary to use a spring on the top of the basket in order to stop the tablets from floating and sticking to the underside of the top of the basket; otherwise testing may result in artificially low values. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

~~Alcohol dose dumping studies:~~

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus ~~1 (basket) @100 rpm,~~(as specified above), with or without alcohol~~;~~ as follows:

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV. Surfactant may not be used in testing in ethanolic media.

If the average release from any timepoints from the test product in alcoholic media show faster release than in 0.1N HCl the need for an in-vivo study must be discussed with FDA.

Dimensions: In accordance with the *Guidance For Industry: Size, Shape and Other Physical Attributes of Generic Tablets and Capsules* the proposed generic product should be no more than 20% larger than the RLD in any single dimension and no more than 40% larger than the volume of the RLD.

Contains Nonbinding Recommendations

Draft Guidance on Hydrocodone Bitartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

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Active Ingredient: Hydrocodone ~~bitartrate~~Bitartrate

Dosage Form; Route: Tablet; extended release; oral

Recommended Studies: Two bioequivalence studies (1—2) and two in-~~-~~vivo comparative

pharmacokinetic (PK) and pharmacodynamic (PD) studies for abuse deterrence assessment (3—4).

1. Type of study: Fasting

Design: Single-dose, two-treatment, two- period crossover in-~~-~~vivo

Strength: ~~20~~120 mg*

Subjects: Males and ~~non-pregnant~~nonpregnant, non-lactating females, general population~~-~~.

Additional Comments: ~~Naltrexone or other opioid antagonist~~ A naltrexone blockade should be ~~incorporated~~used to ~~block~~reduce the ~~pharmacodynamic (PD) effects~~risk of ~~the opioid. The opioid antagonist should be administered well in advance~~any opioid-related adverse events. Administration of ~~opioid dosing to achieve adequate blockade of opioid receptors. The most common approach is to administer~~ 50 mg of naltrexone with 240 mL of water at the following times: (1) 12 hours prior to dosing; (2) at the time of ~~study drug~~ dosing; and (3) 12, 24 and 36 hours after the last dose of study drug. ~~Consult~~Please consult with a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.

Recommended Oct 2016; Revised Jul 2018

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The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (Cmax, $AUC_{12\text{-}24h}$, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$) should be within the limits of 80-125%, where $AUC_{12\text{-}24h}$ is the area under the plasma concentration vs. time curve from 12 to 24 hours.

*If a 120 mg tablet is not intended to be filed, use the highest dosage strength that will be filed.

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2. Type of study: Fed

Design: Single-dose, two- treatment, two-period crossover in- vivo

Strength: ~~20~~120 mg*

Subjects: Males and ~~non-pregnant~~nonpregnant, non-lactating females, general population.

Additional Comments: See comments in Study 1.

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3. Type of study: Fasting, comparative oral PK study of chewed drug products

~~3.~~ Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 60 mg

Subjects: Males and ~~non-pregnant~~nonpregnant, non-lactating females, general population.

Additional ~~Comments~~comments: See comments in Study 1. ~~Patient~~ Relevant chewing conditions include vigorous chewing with molars for three minutes. Additional relevant chewing conditions that can discriminate between test and reference products' ability ~~of deterring~~to deter chewing should be identified~~.~~ and justified. Determine relevant PK parameters including maximum concentration (Cmax), area-–under-the-curve ($AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$), partial-area-under-the-curve ($AUC_{0\text{-}1\ 5h}$, $AUC_{0\text{-}3h}$, and $AUC_{0\text{-}6h}$), and time to maximum concentration (Tmax).
~~Applicants should submit partial AUCs (e.g., $AUC_{0\ 3\ hours}$ and AUC_{0}~~

~~4 hours) as supportive data.~~

Recommended Oct 2016; Revised Jul 2018

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~~4.~~ . Type of study: Fasting, comparative nasal PK and PD study with physically manipulated drug products, consistent with the recommendations in FDA's guidance, "~~"~~*General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*~~,"~~, for tier 2 evaluation of abuse by insufflation as applicable

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 60 mg

Subjects: Non-dependent recreational opioid users, general population[1].

Additional ~~Comments: See all~~ comments ~~in Study 1.~~: Take scientifically appropriate and ethical steps to protect human subjects. This should include ensuring that each subject is not physically dependent on opioids (e.g., through a naloxone challenge test) and has not been seeking or undergoing treatment for abuse of controlled substances such that participating in the study could make them vulnerable to relapse.~~[2]~~ ~~Also see comments on PK parameters in Study 3.~~ Pulverize test ("T") and reference ("R") products to a particle size range that is considered safe and tolerable for human insufflation studies. Characterize the formulation recovery, drug content, and particle size distribution of physically manipulated ~~test~~T and ~~reference~~R drug products used in the nasal ~~PK~~insufflation study using validated analytical procedures. Determine relevant PK parameters including maximum concentration (Cmax), area-under-the-curve (AUC_{0-t}, and $AUC_{0-\infty}$), partial-area-under-the-curve (AUC_{0-15h}, AUC_{0-3h}, and AUC_{0-6h}), and time to maximum concentration (Tmax).

Determine relevant PD parameters on a visual analog scale (VAS) bipolar scale including "Drug Liking" and "Take Drug Again." Details of PD study to be agreed with the agency prior to conducting study.

Analytes to measure (in appropriate biological fluid): Hydrocodone in plasma

Bioequivalence based on (90% CI): Hydrocodone

Abuse deterrence PK based on (upper 95% confidence bound): Hydrocodone

Abuse deterrence PD: Emax (maximum Drug Liking) and Take Drug Again no higher than R product.

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Waiver request of in-vivo testing: 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 100 mg ~~and 120 mg~~(if being filed) based on (i) acceptable bioequivalence studies on the ~~20 mg~~highest strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. If either (ii) or (iii) are not met then the fifth study must be completed.

5. Type of study: Fasted dose Proportionality

Design: Single-dose, crossover in-vivo

Strengths: All

Subjects: Healthy males and non-pregnant, non-lactating females, general population.

Additional Comments: Please see the comments on naltrexone blockade for Study 1. The dose proportionality study may be performed as a single study or divided into multiple studies where the studies are connected by a common strength.

Abuse Deterrence ~~Evaluation~~

Evaluating the Abuse-Deterrence: Since the FDA has determined that the reference listed drug ~~(RLD)~~ for hydrocodone bitartrate extended-release tablet ~~(NDA 206627)~~ has abuse-deterrent properties ~~that are expected to deter abuse~~ (as described in ~~Section~~section 9.2 of the approved Full Prescribing Information), ~~you~~the sponsor of a proposed generic version is required to conduct testing to demonstrate that the proposed generic product is no less abuse-deterrent than the reference listed drug with respect to all potential routes of abuse. The sponsor of a proposed generic version of the reference listed drug should refer to the guidance~~,~~ " for industry *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*~~," regarding the studies that should be conducted to demonstrate that the proposed generic product is no less abuse-deterrent than the RLD with respect to all potential routes of abuse.~~ for general information. Consistent with the guidance, the potential ~~abbreviated new drug application~~ (ANDA) applicants should consider, among other things, the following:

~~a) Conducting all in-vitro abuse deterrence studies using a bracketing design based on appropriate justification (e.g., extremes of the ratios of opioid to excipients contributing to abuse deterrence) or the highest strength based on compositional proportionality of the proposed generic formulations across all strengths.~~

~~[1] This means non-dependent recreational opioid users from the general population who have experience in the use of opioids for non-therapeutic purposes.~~

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[2] For criteria on evaluating substance dependence, refer to, for example, the latest version of *Diagnostic and Statistical Manual of Mental Disorders*, Arlington, VA, American Psychiatric Association

(a) Testing all strengths of T and R products in all in-vitro tests. Alternatively, if the applicant wishes to use a bracketing design, the proposed design and justification should be discussed with the Agency.

~~b)~~ (b) Conducting all in vitro abuse deterrence studies comparing the test and reference products using an intermediate manipulation method (e.g., cutting, grating), in addition to "intact and most effectively physically manipulated drug products" as described in the general guidance.

~~c)~~ (c) Specifying and justifying the total number of tablet units used in ~~a~~each manipulation run (e.g., milling). Justification should address the efficiency of the manipulation, the total percentage lost, the purpose of the manipulation, and the need for the particular manipulation to reflect anticipated actual abuse scenarios.

(d) Specifying and justifying the tools used for physical manipulation and the intervals at which each is replaced during in vitro testing.

~~d)~~ (e) Determining the drug content in manipulated drug products (e.g.~~,~~ cut, grated~~,~~ or milled) and quantifying the drug loss in samples prior to evaluating extractability.

Number of replicates: Minimum 3 per in-vitro test.

Physical Manipulation and Extractability

Physical Manipulation:

Determine the most effective method for particle size reduction of T and R products. Manipulation techniques evaluated must be determined based on the properties of the T and R products, taking into account their formulation designs. This evaluation should include at a minimum: mortar and pestle, cutting, grating, and use of an electronic mill.

Compare the time, difficulty, and particle size distribution achieved with each technique.

Acceptance criteria: Effective particle size reduction of T product cannot be possible using a lower energy particle size reduction method than necessary to achieve comparable particle size reduction of the R product in less than five minutes (e.g., a T product that can be effectively manipulated with a mortar and pestle fails).

Extractablity:

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Conduct extractability tests on T and R products using the methods detailed in Appendix 1 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*. Conduct testing on intact and physically manipulated T and R products, with shaking at a minimum of 150 rpm in 240 ml of solvent, and evaluate the results in accordance with Appendix 1 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*.

Solvents (minimum): Test the following solvents regardless of the percent of opioid drug substance extracted from R product at 30 minutes: deionized water, commercially available food grade vinegar, carbonated drink (pH 2-3), 0.2% baking soda solution, 40% and 95% ethanol, plus any readily available ingestible solvents anticipated to be more effective than those listed above in defeating T product, based on the formulation and properties of T product.

Temperature: RT and ET (boiling temperature of solvents used)

Acceptance criteria: Mean % released from intact and manipulated T product must be less than or equal to mean % released from intact and manipulated R product in same solvent, or in water + 10%, respectively.

Abuse by Injection (parenteral route)

For T and R products, test: Intact tablets with no thermal pretreatment and with thermal pretreatment and physically manipulated products with no thermal pretreatment and with thermal pretreatment.

Thermal pretreatment: For thermal pretreatment of tablets and physically manipulated materials, pretreatment conditions should be selected based on the time and temperature combination anticipated to maximally increase extraction without causing significant degradation. Optimal time and duration of thermal pretreatment may be different for T and R products and for intact and physically manipulated products. For physically manipulated samples, the thermal pretreatment is applied after physical manipulation.

Solvents: Tier 1: Deionized Water. Tier 2: 40% and 95% ethanol, plus any solvents anticipated to be effective in defeating T product, based on the formulation and properties of T product. Solvents tested must include food grade vinegar and 0.2% baking soda if T product has a pH mediated controlled-release mechanism.

Temperature: RT and ET (boiling temperature of solvents used)

Volume: 2 ml, 5 ml, 10 ml

Needle: 18G, 27G

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Extraction Times: Intact 30 mins; Manipulated 5 mins, 30 mins.

Agitation: Shaking (200 rpm), no agitation.

Additional Comments: Determine drug content of the liquid drawn into a syringe and expelled through the needle.

Acceptance criteria – Mean % expelled from T must be less than or equal to mean % expelled from R in same solvent or in in Deionized Water + 5%, respectively. Applied to all test conditions and times. Only required to Test Tier 2 if T passes Tier 1.

Abuse by Insufflation (nasal route)
In-vitro:

Follow Decision Tree 7 in Appendix 4 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*.

The manipulation condition used to pulverize the T product into particles of the required size range for comparison with R must be the minimum energy method able to achieve this. If this is a lower energy method than needed to achieve the same results for R, then T fails the test.

In-vivo:

Refer to Study 4 above.

Abuse by Smoking (inhalation route)

Follow Appendix 5 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*.

Dissolution test method and sampling times:

The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: ~~http://www.accessdata.fda.gov/scripts/cder/dissolution/~~ http://www.accessdata fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products. ~~Specifications will be determined upon review of the ANDA.~~

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Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. ~~Include~~For reference product, it is necessary to use a spring on the top of the basket in order to stop the tablets from floating and sticking to the underside of the top of the basket; otherwise testing may result in artificially low values. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released to provide assurance against premature release of drug (dose dumping) from the formulation.

Alcohol dose dumping studies:

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP ~~Apparatus I (basket) @100 rpm,~~apparatus (as specified above), with or without alcohol~~,~~ as follows:

Test 1: 12 units tested ~~per~~according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV. Surfactant may not be used in testing in ethanolic media.

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If the average release from any timepoints from the test product in alcoholic media show faster release than in 0.1N HCl the need for an in-vivo study must be discussed with FDA.

Dimensions:

In accordance with the *Guidance For Industry: Size, Shape and Other Physical Attributes of Generic Tablets and Capsules* the proposed generic product should be no more than 20% larger than the RLD in any single dimension and no more than 40% larger than the volume of the RLD.

Studies must be conducted on the proposed generic product to demonstrate that the initial tablet size, and swelling of the dosage form on hydration do not present a greater risk of esophageal or gastrointestinal obstruction than the reference product.

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Contains Nonbinding Recommendations

Draft Guidance on Hydrocodone Bitartrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Hydrocodone Bitartrate

Dosage Form; Route: Tablet; extended release; oral

Recommended Studies: Two bioequivalence studies (1-2) and two in-vivo comparative pharmacokinetic (PK) and pharmacodynamic (PD) studies for abuse deterrence assessment (3-4).

1. Type of study: Fasting

Design: Single-dose, two-treatment, two period crossover in-vivo

Strength: 120 mg*

Subjects: Males and nonpregnant, non-lactating females, general population.

Additional Comments: A naltrexone blockade should be used to reduce the risk of any opioid-related adverse events. Administration of 50 mg of naltrexone with 240 mL of water at the following times: (1) 12 hours prior to dosing; (2) at the time of dosing; and (3) 12, 24 and 36 hours after the last dose of study drug. Please consult with a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist.

The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (Cmax, $AUC_{12\text{-}24h}$, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$) should be within the limits of 80-125%, where $AUC_{12\text{-}24h}$ is the area under the plasma concentration vs. time curve from 12 to 24 hours.

*If a 120 mg tablet is not intended to be filed, use the highest dosage strength that will be filed.

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2. Type of study: Fed

Design: Single-dose, two treatment, two-period crossover in-vivo

Strength: 120 mg*

Subjects: Males and nonpregnant, non-lactating females, general population.

Additional Comments: See comments in Study 1.

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3. Type of study: Fasting, comparative oral PK study of chewed drug products

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 60 mg

Subjects: Males and nonpregnant, non-lactating females, general population.

Additional comments: See comments in Study 1. Relevant chewing conditions include vigorous chewing with molars for three minutes. Additional relevant chewing conditions that can discriminate between test and reference products' ability to deter chewing should be identified and justified. Determine relevant PK parameters including maximum concentration (Cmax), area-under-the-curve (AUC_{0-t}, and $AUC_{0-\infty}$), partial-area-under-the-curve ($AUC_{0-1.5h}$, AUC_{0-3h}, and AUC_{0-6h}), and time to maximum concentration (Tmax).

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4. Type of study: Fasting, comparative nasal PK and PD study with physically manipulated drug products, consistent with the recommendations in FDA's guidance, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*, for tier 2 evaluation of abuse by insufflation as applicable

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 60 mg

Subjects: Non-dependent recreational opioid users, general population.

Additional comments: Take scientifically appropriate and ethical steps to protect human subjects. This should include ensuring that each subject is not physically dependent on opioids (e.g., through a naloxone challenge test) and has not been seeking or undergoing treatment for abuse of controlled substances such that participating in the study could make them vulnerable to relapse. Pulverize test ("T") and reference ("R") products to a

particle size range that is considered safe and tolerable for human insufflation studies. Characterize the formulation recovery, drug content, and particle size distribution of physically manipulated T and R drug products used in the nasal insufflation study using validated analytical procedures. Determine relevant PK parameters including maximum concentration (Cmax), area-under-the-curve (AUC_{0-t}, and $AUC_{0-\infty}$), partial-area-under-the-curve ($AUC_{0-1.5h}$, AUC_{0-3h}, and AUC_{0-6h}), and time to maximum concentration (Tmax).

Determine relevant PD parameters on a visual analog scale (VAS) bipolar scale including "Drug Liking" and "Take Drug Again." Details of PD study to be agreed with the agency prior to conducting study.

Analytes to measure (in appropriate biological fluid): Hydrocodone in plasma

Bioequivalence based on (90% CI): Hydrocodone

Abuse deterrence PK based on (upper 95% confidence bound): Hydrocodone

Abuse deterrence PD: Emax (maximum Drug Liking) and Take Drug Again no higher than R product.

Waiver request of in-vivo testing: 20 mg, 30 mg, 40 mg, 60 mg, 80 mg and 100 mg (if being filed) based on (i) acceptable bioequivalence studies on the highest strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. If either (ii) or (iii) are not met then the fifth study must be completed.

5. Type of study: Fasted dose Proportionality

Design: Single-dose, crossover in-vivo

Strengths: All

Subjects: Healthy males and non-pregnant, non-lactating females, general population.

Additional Comments: Please see the comments on naltrexone blockade for Study 1. The dose proportionality study may be performed as a single study or divided into multiple studies where the studies are connected by a common strength.

Abuse Deterrence

Evaluating the Abuse-Deterrence: Since the FDA has determined that the reference listed drug for hydrocodone bitartrate extended release tablet has abuse-deterrent properties (as described in section 9.2 of the approved Full Prescribing Information), the sponsor of a proposed generic version is required to conduct testing to demonstrate that the proposed generic product is no less abuse-deterrent than the reference listed drug with respect to all potential routes of abuse. The sponsor of a proposed generic version of the reference listed drug should refer to the guidance for industry *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products* for general information. Consistent with the guidance, the potential ANDA applicants should consider, among other things, the following:

(a) Testing all strengths of T and R products in all in-vitro tests. Alternatively, if the applicant wishes to use a bracketing design, the proposed design and justification should be discussed with the Agency.

(b) Conducting all in vitro abuse deterrence studies comparing the test and reference products using an intermediate manipulation method (e.g., cutting, grating), in addition to "intact and most effectively physically manipulated drug products" as described in the general guidance.

(c) Specifying and justifying the total number of tablet units used in each manipulation run (e.g., milling). Justification should address the efficiency of the manipulation, the total percentage lost, the purpose of the manipulation, and the need for the particular manipulation to reflect anticipated actual abuse scenarios.

(d) Specifying and justifying the tools used for physical manipulation and the intervals at which each is replaced during in vitro testing.

(e) Determining the drug content in manipulated drug products (e.g. cut, grated or milled) and quantifying the drug loss in samples prior to evaluating extractability.

Number of replicates: Minimum 3 per in-vitro test.

Physical Manipulation and Extractability

Physical Manipulation:

Determine the most effective method for particle size reduction of T and R products. Manipulation techniques evaluated must be determined based on the properties of the T and R products, taking into account their formulation designs. This evaluation should include at a minimum: mortar and pestle, cutting, grating, and use of an electronic mill.

Compare the time, difficulty, and particle size distribution achieved with each technique.

Acceptance criteria: Effective particle size reduction of T product cannot be possible using a lower energy particle size reduction method than necessary to achieve comparable particle size reduction of the R product in less than five minutes (e.g., a T product that can be effectively manipulated with a mortar and pestle fails).

Extractablity:

Conduct extractability tests on T and R products using the methods detailed in Appendix 1 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*. Conduct testing on intact and physically manipulated T and R products, with shaking at a minimum of 150 rpm in 240 ml of solvent, and evaluate the results in accordance with Appendix 1 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*.

Solvents (minimum): Test the following solvents regardless of the percent of opioid drug substance extracted from R product at 30 minutes: deionized water, commercially available food grade vinegar, carbonated drink (pH 2-3), 0.2% baking soda solution, 40% and 95% ethanol, plus any readily available ingestible solvents anticipated to be more effective than those listed above in defeating T product, based on the formulation and properties of T product.

Temperature: RT and ET (boiling temperature of solvents used)

Acceptance criteria: Mean % released from intact and manipulated T product must be less than or equal to mean % released from intact and manipulated R product in same solvent, or in water + 10%, respectively.

Abuse by Injection (parenteral route)

For T and R products, test: Intact tablets with no thermal pretreatment and with thermal pretreatment and physically manipulated products with no thermal pretreatment and with thermal pretreatment.

Thermal pretreatment: For thermal pretreatment of tablets and physically manipulated materials, pretreatment conditions should be selected based on the time and temperature combination anticipated to maximally increase extraction without causing significant

degradation. Optimal time and duration of thermal pretreatment may be different for T and R products and for intact and physically manipulated products. For physically manipulated samples, the thermal pretreatment is applied after physical manipulation.

Solvents: Tier 1: Deionized Water. Tier 2: 40% and 95% ethanol, plus any solvents anticipated to be effective in defeating T product, based on the formulation and properties of T product. Solvents tested must include food grade vinegar and 0.2% baking soda if T product has a pH mediated controlled-release mechanism.

Temperature: RT and ET (boiling temperature of solvents used)

Volume: 2 ml, 5 ml, 10 ml

Needle: 18G, 27G

Extraction Times: Intact 30 mins; Manipulated 5 mins, 30 mins.

Agitation: Shaking (200 rpm), no agitation.

Additional Comments: Determine drug content of the liquid drawn into a syringe and expelled through the needle.

Acceptance criteria – Mean % expelled from T must be less than or equal to mean % expelled from R in same solvent or in in Deionized Water + 5%, respectively. Applied to all test conditions and times. Only required to Test Tier 2 if T passes Tier 1.

Abuse by Insufflation (nasal route)
In-vitro:

Follow Decision Tree 7 in Appendix 4 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*.

The manipulation condition used to pulverize the T product into particles of the required size range for comparison with R must be the minimum energy method able to achieve this. If this is a lower energy method than needed to achieve the same results for R, then T fails the test.

In-vivo:

Refer to Study 4 above.

Abuse by Smoking (inhalation route)

Follow Appendix 5 of *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*.

Dissolution test method and sampling times:

The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.

Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. For reference product, it is necessary to use a spring on the top of the basket in order to stop the tablets from floating and sticking to the underside of the top of the basket; otherwise testing may result in artificially low values. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Alcohol dose dumping studies:

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus (as specified above), with or without alcohol as follows:

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV. Surfactant may not be used in testing in ethanolic media.

If the average release from any timepoints from the test product in alcoholic media show faster release than in 0.1N HCl the need for an in-vivo study must be discussed with FDA.

Dimensions:

In accordance with the *Guidance For Industry: Size, Shape and Other Physical Attributes of Generic Tablets and Capsules* the proposed generic product should be no more than 20% larger than the RLD in any single dimension and no more than 40% larger than the volume of the RLD.

Studies must be conducted on the proposed generic product to demonstrate that the initial tablet size, and swelling of the dosage form on hydration do not present a greater risk of esophageal or gastrointestinal obstruction than the reference product.